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ADVANCEMENTS IN TARGETED THERAPIES FOR RHEUMATOID ARTHRITIS: A COMPARATIVE REVIEW OF CONVENTIONAL AND BIOLOGICAL DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS

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ABSTRACT: Rheumatoid arthritis (RA) is an autoimmune disease that causes progressive joint damage and systemic complications, leading to significant physical and socioeconomic impacts. Conventional treatments such as nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying anti-rheumatic drugs (DMARDs) often fail to halt disease progression and prevent cartilage erosion. The review compares conventional therapies with emerging biological DMARDs (bDMARDs) and explores novel therapeutic targets. The advent of bDMARDs in targeting key inflammatory cytokines, such as Janus kinase (JAK), Tumour Necrosis Factor-alpha (TNF-α), and Bruton's Tyrosine Kinase (BTK), have significantly improved clinical outcomes. Promising agents such as JAK inhibitors (Tofacitinib, Baricitinib), TNF-α blockers (Adalimumab, Etanercept), and BTK inhibitors are under clinical trials, highlighting the potential of targeted therapies in immune modulation. Most of the compounds possess a heterocycle, especially pyridine scaffold, emphasizing the importance of heterocycle to potentiate drug-receptor interaction. Additionally, this paper mentions the rise of innovative therapies, such as Mesenchymal Stem Cell (MSC) therapy, the DEN-181 immune modulation vaccine, and vagus nerve stimulation devices, which focus on tissue regeneration and novel immune pathways. The explored scaffolds, structure-activity relationships, and pharmacological evaluation of small molecule inhibitors and biologics will provide insights for the design of new chemical entities for potential and plausible RA targets. This comprehensive review emphasizes the paradigm shift towards precision medicine, offering a roadmap for integrating combination therapies and novel immunomodulatory approaches for holistic RA management.

INTRODUCTION: Rheumatoid arthritis (RA) is an inflammatory autoimmune disease that leads to gradual articular and periarticular damage involving several joints in a symmetric pattern. It also causes inflammation, variations in joint integrity and destruction of synovial joints, subchondral bones, tendons and ligaments [1].

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The occurrence of RA in middle-aged females have been observed two to three times greater than in men. A positive family history increases the risk of rheumatoid arthritis roughly three to five times [2]. Overall, RA is associated with disability, systemic complications along with socioeconomic costs [3].

Approximately worldwide, 18 million people were affected by rheumatoid arthritis in 2020, a significant increase from 1990, when the figure stood at around 12 million [4]. About 70% of the population suffering from rheumatoid arthritis are women, and 55% of them are older than 55 years. 13 million RA patients experienced severity levels (moderate or severe) that could benefit from

rehabilitation [4, 5]. Globally, the number of rheumatoid arthritis cases is expected to increase by 40% by 2050, aligned with the aging global population and shifting risk factors. The projected increase in India aligns with global trends, with the number of patients expected to exceed 6.5 million by 2050 [6]. Despite the availability of many antirheumatic drugs, this disease is still not well managed in up to 30% of RA patients [6, 7]. These factors necessitate the need to explore drugs in this therapeutic area.

Pathogenesis and Targets Involved: During the disease progression, leucocytes penetrate the synovial membrane and inflammatory cytokines enter the synovial fluid. This causes long-lasting synovitis which in turn produces autoantibody and furthermore, decreased reactive antigen species boosts pro-inflammatory mediators thus, precipitating the condition. In the pathogenesis pathway, fibroblast-like synoviocytes (FLSs) interact with innate immune system cells (mast cells, dendritic cells, and monocytes/macrophages) and adaptive immune system cells (T-lymphocytes and B-cells) in the pathogenesis pathway, which triggers the inflammatory process **Fig. 1**.

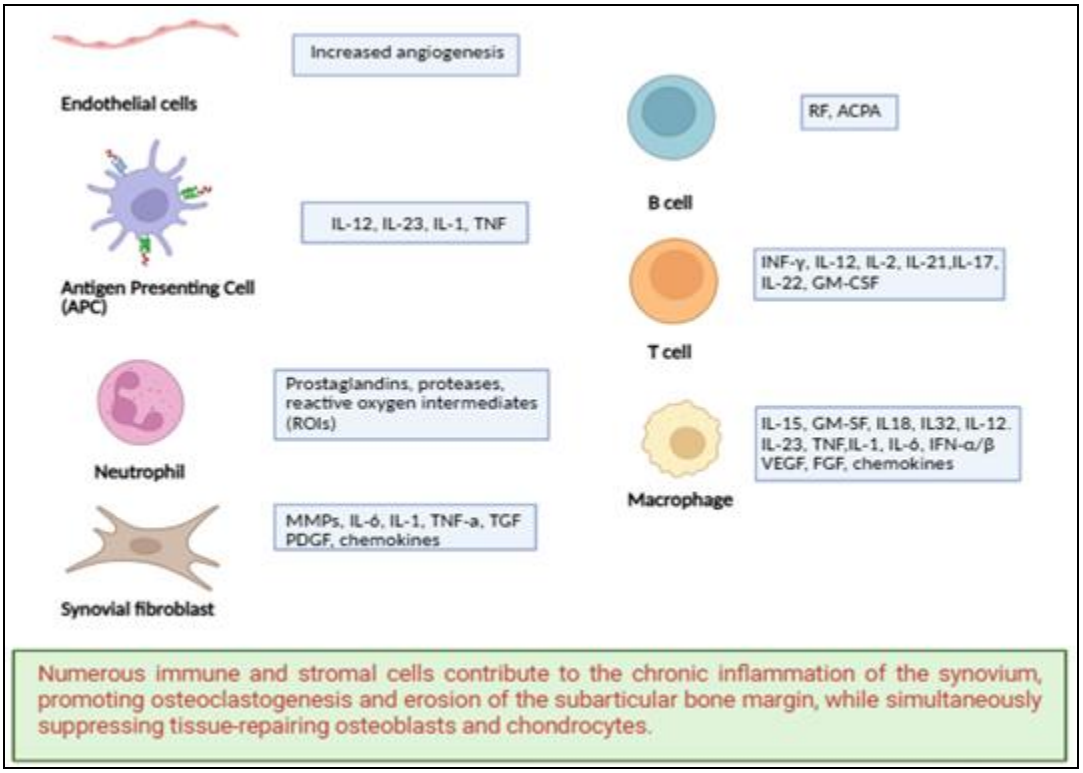

FIG. 1: ROLE OF NUMEROUS CELLS AND THEIR CYTOKINES IN THE PROGRESSION OF RA [8]

These two immune systems are closely involved in the development of an important diagnostic marker for RA, anti-citrullinated protein antibodies (ACPA) that enhances the NF-kB pathway and TNF-α which activates inflammatory responses [8]. Further, the targets involved in the pathogenesis of RA, are discussed here. An influx of Ca^{2+} excites T-cell proliferation and IL2 (interleukin) production, and causes an increase in pro-inflammatory cytokines (IL1, IL6, and TNF-α) levels [9]. Spleen adherent cells (SAC) causes the inhibition of pro-inflammatory chemokines and cytokines production [10]. cPLA2 represents a central enzyme synthesized at the inflammation site and is a mediator of many inflammatory processes [11]. Prostanoid receptor EP2 is stimulated by PGE2 and is a biological target for anti-inflammatory therapy [12]. Therapeutic targets for Th17-(CD4+ T helper (Th) cells, which are essential effectors of the immune response and play a critical role in inflammation-related autoimmune disorders like RA, include receptor-related orphan receptor-gamma-t (RORγt) [7, 13]. Protein kinase C theta (PKCθ) has therapeutic potential for T cell-mediated RA and a significant role in T cell signalling [14]. Another intriguing therapeutic target for the management of inflammatory diseases in TNF-mediated inflammation is receptor interacting

protein 1 (RIP1) kinase [15]. The release of pro-inflammatory cytokines, TNF and IL, is regulated by the p38 mitogen-activated protein (MAP) kinase [16]. A crucial process in lipid peroxidation is the generation of free radicals which are directly associated in numerous diseases such as atherosclerosis, rheumatoid arthritis [17]. Drug development process has been greatly aided by knowledge about the pathophysiology and the mode of action of these particular immune-targeted therapies. They have identified the immunological pathways responsible for comorbidities and articular inflammation [8].

Therapies Available to Treat RA: The current strategies for treatment and management of RA are nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids and disease-modifying antirheumatic drugs (DMARDs) **Fig. 2** and **3**. Conventional synthetic DMARDs (csDMARDs) include methotrexate (MTX), sulfasalazine, and leflunomide [11]. The remission rate is higher when corticosteroids have been administered with a csDMARD (usually MTX), than alone (44.8% to 76.7% for combination therapy and 27.8% to 33.3% for MTX monotherapy) [7, 8]. Despite the success of csDMARDs still there are some setbacks. It was claimed by Doan *et al.* that hepatotoxic effects were associated with the combination therapy of leflunomide with methotrexate than treatment with either drug alone [18]. Conventional drugs exert their onset after several weeks (such as MTX) or months (such as gold salts) [19]. The active metabolite malononitrile amide A77 1726 of the prodrug, leflunomide increases the risk of teratogenic effects [20].

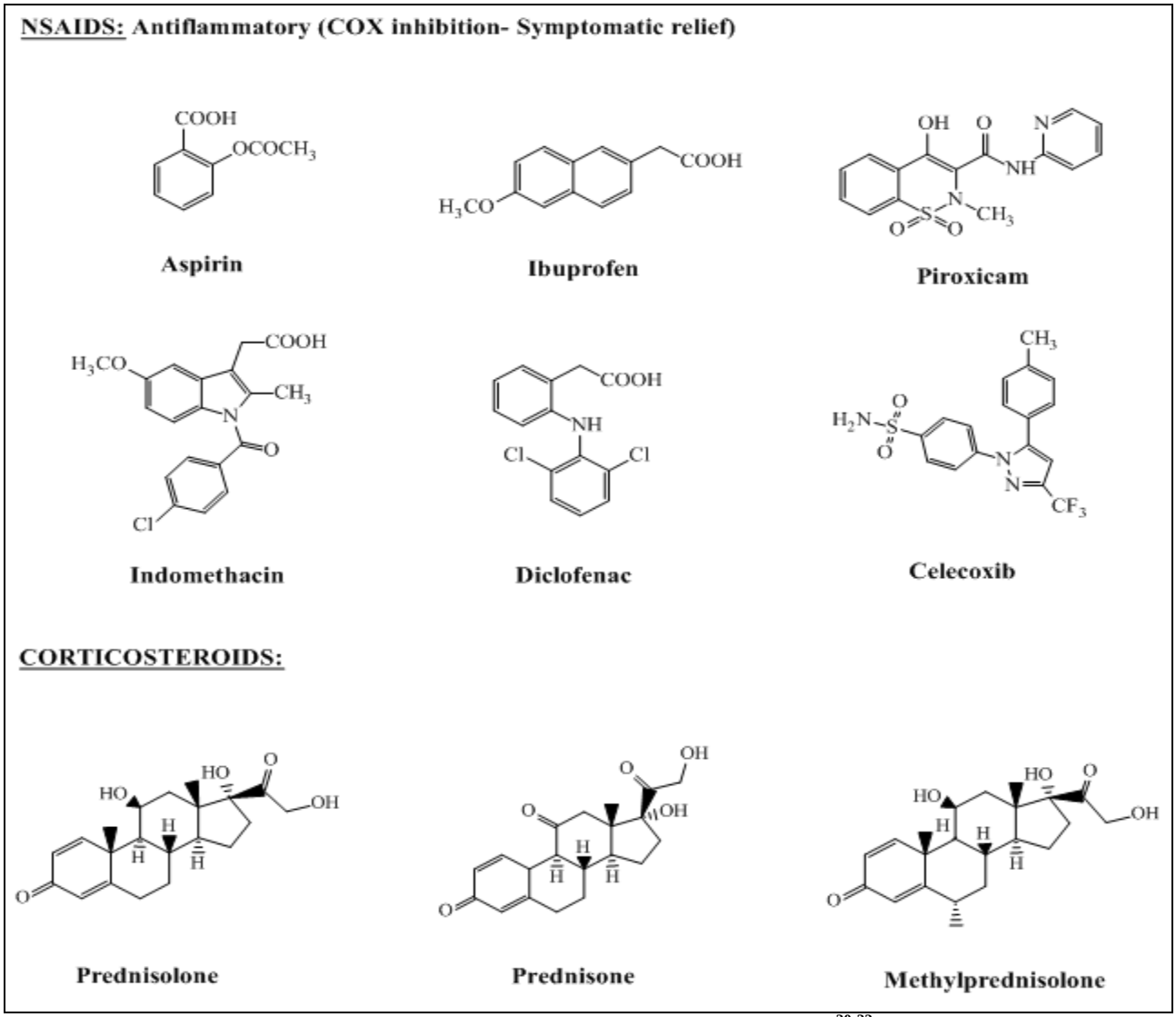

FIG. 2: CONVENTIONAL THERAPIES FOR RA [20-22]

These setbacks forced the researchers to search for new therapeutic approaches and biological DMARDs are one of them. Current tools of molecular and cell biology which have been recognized as promising molecules are the biological DMARDs, which can be targeted for RA treatment. The biological DMARDs target many inflammatory cytokines like TNF-α (Tumour necrosis factor-α), JAK (Janus Kinase), BTK (Bruton Tyrosine Kinase), Interleukins (IL) and have proven to be the most effective treatments over conventional DMARDs. In the past year, the development of effective biologics and small-molecule kinase have shown better clinical results for RA [23]. This mini-review focuses on the molecules which are established, under pipeline and in clinical studies for JAK, TNF-α and BTK inhibitors. It will provide an overview of structural and chemical strategies for designing and developing lead potent molecules.

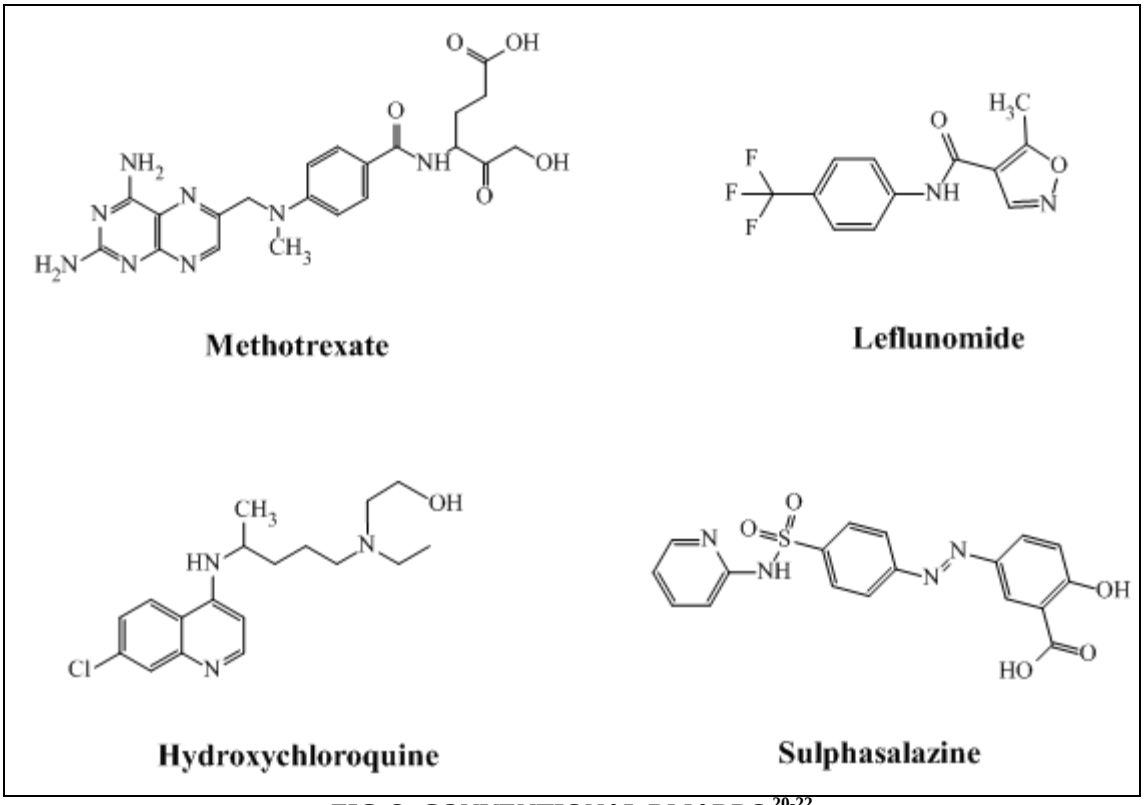

FIG. 3: CONVENTIONAL DMARDS [20-22]

Biological DMARDs and Their Importance: At present there are nine different biologic therapies available *viz*, seven are inhibitors of pro-inflammatory cytokines (five targets tumour necrosis factor [TNF], one targets interleukin IL1 and one targets IL6), also agents that target T- and B-lymphocyte. All of these medications are first- or second-line approved therapies in patients who have not reacted to conventional DMARDs, as well as to first-line therapy in many circumstances [21]. Recombinant biologic molecules that can identify receptors on the cell surface or extracellular molecules with high specificity are called biologic DMARDs (bDMARDs). The bDMARDs are approved as monotherapy in the treatment of RA by the European Medicines Agency (EMA) or United States Food and Drug Administration (FDA). They include the tumour necrosis factor (TNF) inhibitors: certolizumab pegol (CZP, 1998), etanercept (ETN, 1998), infliximab (IFX, 1999), adalimumab (ADA, 2002) [20-24]. When TNF biologic therapy (adalimumab [ADA]) is compared with csDMARDs (MTX) only, the combination treatment led to better response and remission [9]. A comparative overview of biological treatment over conventional ones gives us a brief insight of their disease-modifying therapeutic potential over symptomatic relief. Hence, we intend to compile information on promising hits and leads explored to inhibit JAK, TNF-α and BTK for RA treatment from a chemist's point of view.

Biological Targets:

Janus Kinase (JAK) Inhibition: Small-molecule DMARDs have transformed the RA treatment. Among other tyrosine kinases, the Janus kinases (JAKs) are involved in signal transduction by binding to interleukins (including IL2, IL6, IL12, IL15, *etc*) receptors [24]. Tyrosine kinase family has JAK which comprises a group of four intracellular enzymes viz JAK1, JAK2, JAK3, and TYK2 [24, 25]. Type 1 interferon signal transduction is regulated by JAK1. JAK2 interacts with cytokines and other hormones through the glycoprotein-130 subunits. Due to this, JAK2 inhibitor use has been linked to anaemia and thrombocytopenia. Through the common γ chain receptor subunit, JAK3 interacts with many inflammatory cytokines [24]. Therefore, it is needed to synthesize a new selective inhibitor against a single JAK isozyme. For the treatment of rheumatoid arthritis, among the four isozymes, JAK1 is important because of its ability to efficiently maintain the cytokines level involved in the disease symptoms than the other JAK [26]. Tofacitinib, approved by the US FDA in 2012 which was developed by Pfizer, is thought to work by inhibiting Janus kinases (JAKs). It is a pan-JAK inhibitor that can suppress all JAK isozymes but preferably it inhibits JAK-1 and JAK-2 [27]. Synthetic compounds like tofacitinib (TOFA, Compound 1, IC_{50}: 3.1nM) and baricitinib (BARI, Compound 2, IC_{50}**:** 5.9nM) were mainly synthesised to target the JAKs, are defined as targeted synthetic DMARDs (tsDMARDs) **Fig. 4** [8]. All JAK-1 inhibitor marketed drugs are nitrogen-containing heterocyclic compounds. Compounds 1 and 2 both possess a pyrrolo-pyrimidine ring. Filgotinib (GLPG0634), upadacitinib (ABT-494, Compound 3, IC_{50} of 0.045 µM), solcitinib (GSK2586184), itacitinib (INCB039110), PF-04965842 are the representative JAK1- selective inhibitors. JAK-3 selective inhibitors are peficitinib and decernotinib **Fig. 4** [28]. According to Yoshiya Tanaka *et al*, Peficitinib (Compound 4) is a JAK-3 selective inhibitor for the treatment of RA which is approved in Japan and Korea. Drugs under clinical trials are all JAK-1 inhibitors. Itacitinib (Compound 5) (JAK-1, IC_{50}:10nM) is in phase II clinical trial, Filgotinib Compound 6 under phase III, Solcitinib (Compound 7) and PF-04965842 (Compound 8) clinical trial studies are being conducted by GlaxoSmithKline and Pfizer for evaluating its inflammatory activity. Derocitinib (Compound 9) is also in phase II of its clinical trial. 3(R)-(3-methyl-(7H-pyrrolo[2,3-d] pyrimidin-4-yl) amine) pyrrolidine-3-oxopropanenitrile (compound 10, IC_{50}:3.1nM) and 1H-pyrrolo[2,3-b] pyridine-5-carboxamide (compound 11, IC_{50}: 5.1nM) are candidates under pipeline **Fig. 4.** Chemical modification of compound 11 led to a large increase in JAK inhibitor activity and metabolic stability in liver microsomes. Compound 10 is a potential analogue with promising selectivity for JAK1 over JAK 2, 3, and TYK2 and has fewer side effects. Its human liver microsomal stability withstands the liver first pass **Fig. 5** [29].

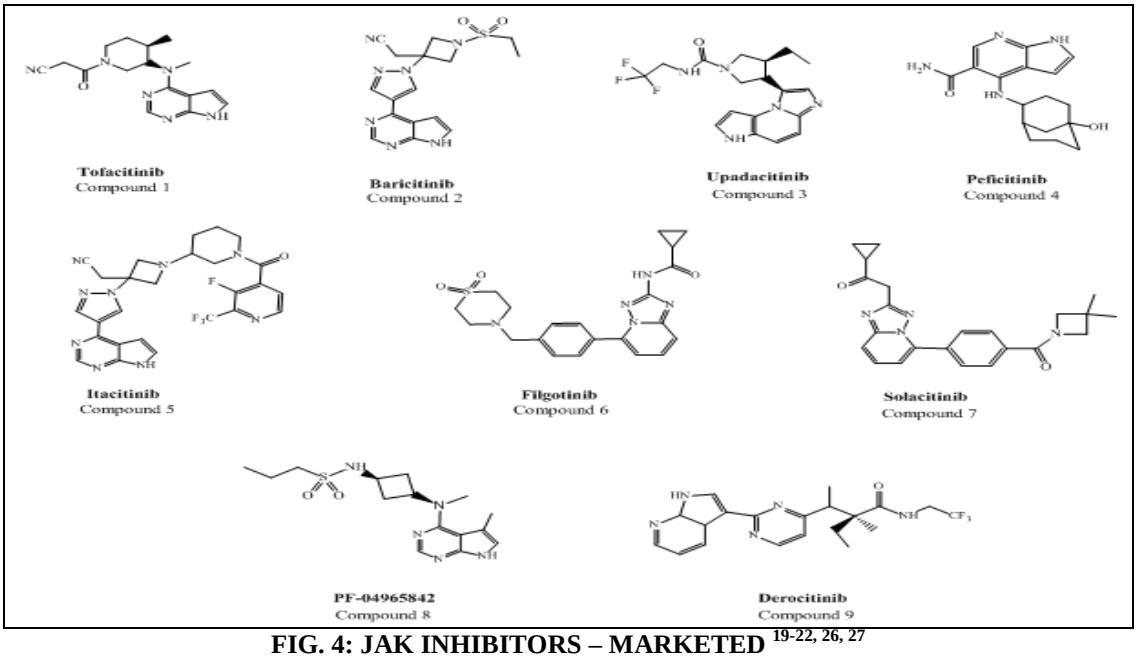

FIG. 4: JAK INHIBITORS – MARKETED [19-22, 26, 27]

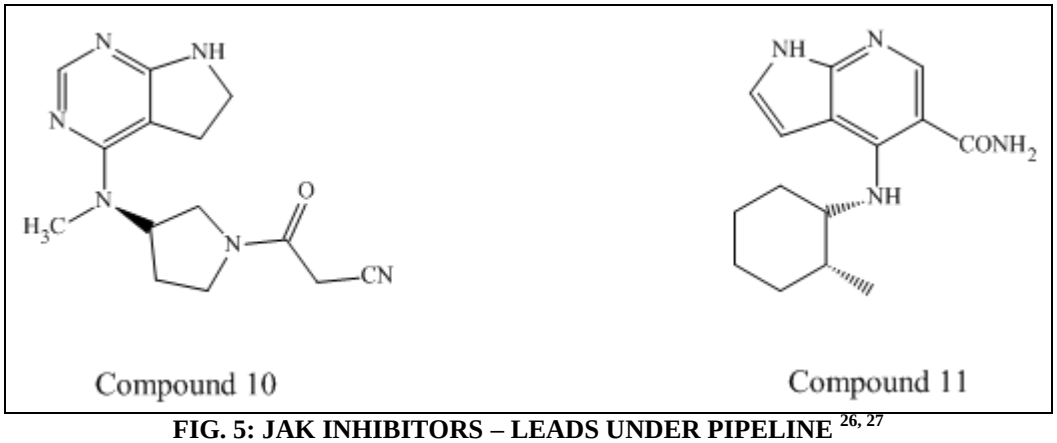

FIG. 5: JAK INHIBITORS – LEADS UNDER PIPELINE [26, 27]

In the past decade, many researcher have focused on the development of heterocyclic small molecule inhibitors with different nucleus such as pyridine, pyrimidine, imidazole, indole, pyrazole, pyrrole and triazine [30]. Gehringer M. *et al* have highlighted the development of novel tricyclic compounds targeting JAK3, and achieved good selectivity and activity. By applying the rigidization method, the 3-methyl-1, 6-dihydrodipyrrolo [2, 3-b:2',3'-d] pyridine scaffold was designed based on the tofacitinib–JAK3 crystal structure [31]. A series of compounds were synthesized containing the tricyclic structure. Compound 12 was found to be the most potent JAK3 inhibitor with an IC_{50} value of 220 pM. as compared to tofacitinib, with IC_{50} values < 3 nM, the lowest concentration evaluated it demonstrated a notable shift in inhibitory efficacy towards STAT5/6 [31]. In 2017, Kaur M. *et al*, have synthesized oxindole derivatives for the inhibition of both JAK3 and SYK. Compound 13 was the most active among the synthesized compounds, and showed better *in-vivo* antiarthritic activity than the standard drug Indomethacin [32].

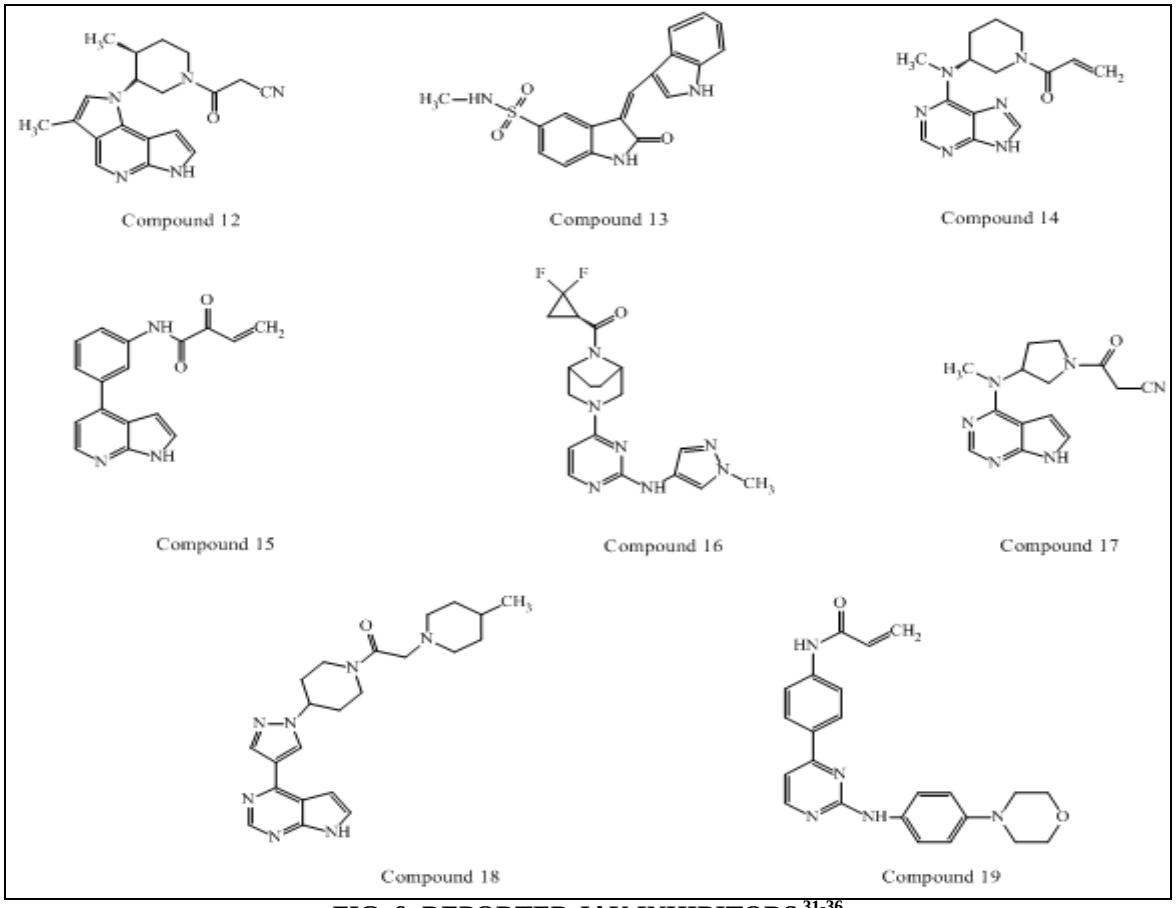

FIG. 6: REPORTED JAK INHIBITORS [31-36]

He L. *et al* developed a highly selective JAK3 covalent inhibitor containing purine heterocycle that targeted Cys909 residue in JAK3. Compound 14 exhibited IC_{50} value of 57 nM demonstrating excellent selectivity. The compound showed potent JAK/STAT inhibition with superior pharmacokinetic properties compared to tofacitinib [33]. The researchers have also synthesized pyrimidine heterocyclic compounds as selective, irreversible covalent JAK3 inhibitors. Compound 15 was found to have the highest selectivity and potency with IC_{50} value of 0.14 nM and showed significant anti-inflammatory activity in mice models [34]. Fensome A. et al described the TYL2 and JAK1-dual inhibitor, containing a constrained piperazinyl-pyrimidine ring. Compound 16 exhibited an excellent off-target polypharmacology and pharmacokinetic profiles consistent with once daily dosing in humans. It showed an IC_{50} value of 23 nM for TYK2 and 17 nM for JAK1. It inhibited the cytokine pathways relevant to RA[35].

Covington. *et al* synthesized a series of 3(R)-aminopyrrolidine compounds exhibiting JAK-1 selective inhibition. Compound 17, showed improved selectivity for JAK1 compared to that of tofacitinib (IC_{50} 11, 2.4 x 10^2, 2.8 x 10^3, and 1.1 x 10^2 nM for JAK1, JAK2, JAK3, and TYK2, respectively) [37]. 4-(1H-pyrazol-4-yl)-7H-pyrrolo [2,3-d] pyrimidine derivatives were synthesized in two series by combining different N-acylpiperidine motifs with baricitinib by Jiang F. *et al*. Compound 18 displayed anti-inflammatory activity by inhibiting LPS-induced NO generation from RAW264.7 macrophages better than reference baricitinib. It exhibited strong inhibition of JAK1 and JAK2 with an IC_{50} of 88.2 μM [36]. Zhou S. *et al* designed and synthesized 4- or 6-phenyl-pyrimidine derivatives as selective JAK3 inhibitors. Compound 19 showed potent JAK3 inhibition (IC_{50} = 1.7 nM) with exceptional selectivity over other JAK isoforms (>588-fold for JAK1 and JAK2) (Fig. 6) [37].

TNF-alpha Inhibition: The start and development of RA and other immune-mediated diseases are dependent on a pro- inflammatory cytokine, tumour necrosis factor. The effectiveness of anti-TNF-biological therapies was demonstrated. Since the discovery of anti-TNF- biologics, much effort has been put into creating a tiny, oral TNF- antagonist. Inflammation can be caused by activated monocytes, macrophages, and T lymphocytes. Local bone loss is caused by elevated levels of TNF-α in inflammatory musculoskeletal disorders. TNF receptors 1 and 2 have different species specificity and varied affinities *via* which TNF-α gets activated. Important signalling pathways, including the NF-κB route, RANKL signalling, the extracellular signal-regulated kinase (ERK) signalling system, the tumour progression locus 2 (TPL2) pathway, and proapoptotic signalling, which can be triggered by the interaction of TNF-α and its receptors [38]. Corticosteroids and disease-modifying anti-rheumatic medications (DMARDs) are the traditional treatment options for RA. Biopharmaceuticals, particularly TNF inhibitors, offer improved chances for disease management with stronger anti-arthritic benefits for patients who do not respond well to these drugs [39]. Hence, there is a need to design and develop more drugs acting through this mechanism.

The marketed TNF-α inhibitors are Infliximab (compound 20), Adalimumab (compound 21), Etanercept (compound 22) **Fig. 7.** and Golimumab. H. E. Seymar *et al* reports usage of Etanercept and Infliximab in the UK to RA patients [40]. Once a month, infliximab is given. INF biosimilars for infliximab, such as IFXdyyb, SB2, CT-P13, BOW015, NI-071, PF-06438179/GP1111, STI-002, and ABP 710, have been approved by few countries. Some countries have approved biosimilars for Adalimumab (Ada), including ZRC-3197, ABP 501,117 Adfrar, and others. Etanercept was developed by Amgen and Wyeth Pharmaceuticals, the permitted biosimilars for it are SB4 and GP2015. It is given twice a week [38, 39].

The soluble and transmembrane bioactive forms of human TNF-α are both bound by the Human Ig G1 kappa monoclonal antibody golimumab. Once a month, it is given subcutaneously. Two golimumab biosimilars that are presently in the preclinical stage are BOW100 and ONS-3035. Certolizumab, a human anti-TNF-α antibody fragment, neutralizes soluble and membrane-linked TNF-α when it is chemically bound to polyethylene glycol. One certolizumab pegol biosimilar that is presently undergoing preclinical phase testing is called PF-688 [41].

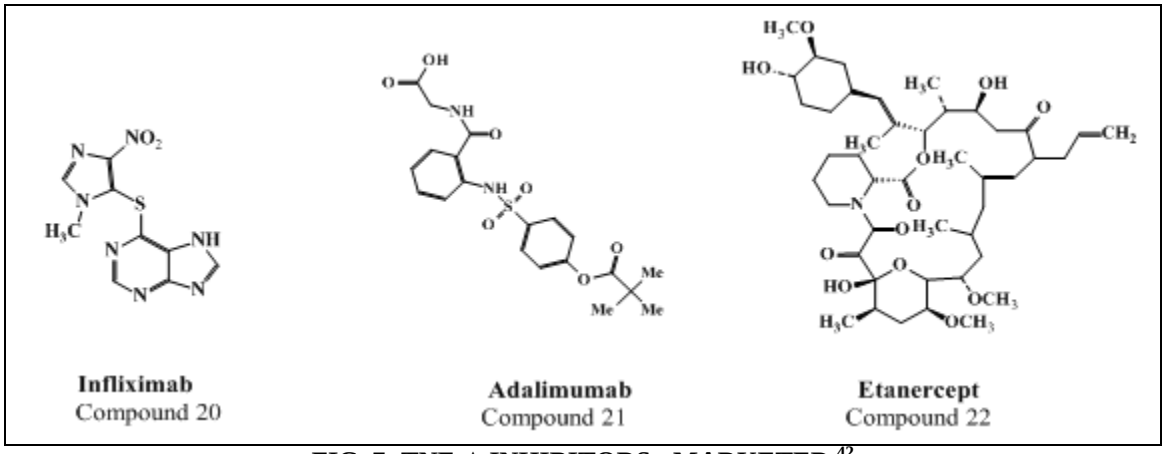

FIG. 7: TNF-A INHIBITORS - MARKETED [42]

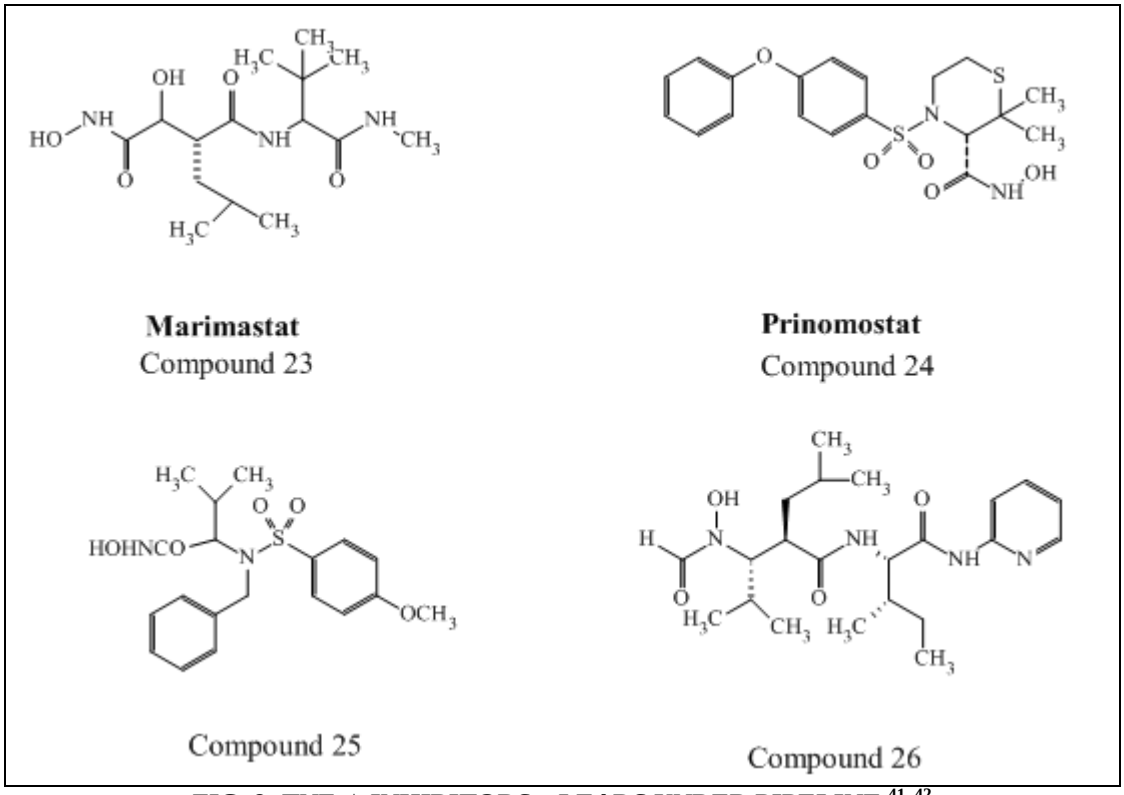

FIG. 8: TNF-A INHIBITORS – LEADS UNDER PIPELINE [41, 42]

The TNF-α converting enzyme (TACE) produces TNF-α, which is a crucial cytokine involved in pathogenesis of RA. TACE is one of the targets to block TNF-α in biological fluid. Marimastat (Compound 23, IC_{50}=3.8 nM), Prinomastat (Compound 24, IC_{50}= 22 nM), CGS-27023A (Compound 25) and GW3333 (Compound 26, IC_{50}: 40nM) drugs are under pipeline to inhibit TACE [42]. The leads under pipeline such as compound 23, 24, 25 and 26 possess primarily amide and sulfonamide moieties **Fig. 8.** The development of small-molecule inhibitors for TNF-α involves a multidisciplinary approach that integrates computational and experimental strategies.

A crucial tool in this approach is molecular docking, which makes it possible to virtually screen extensive compound libraries against TNF-α to find possible leads. By predicting binding affinities and interactions within the active site of TNF-α, docking studies provide valuable insights into structure-activity relationships and facilitate the rational design of inhibitors. Advanced e-pharmacophore modelling and binary QSAR methods further enhance the accuracy of virtual screenings, narrowing down the candidates with optimal pharmacokinetic and toxicity profiles. Techniques such as Claisen–Schmidt [42, 43] condensation and Algar–Flynn–Oyamada [43,

[44]reactions have proven instrumental in constructing bioactive scaffolds. These methods allow precise functional group modifications, essential for optimizing anti-inflammatory activity. The iterative feedback between docking simulations and synthetic experiments accelerates the discovery of effective and selective TNF-α inhibitors, ultimately bridging the gap between computational predictions and biological validation. Hatnapure *et al*. developed a new series of 3-hydroxy-2-(2, 4, 5-trimethoxyphenyl)-4H-chromen-4-one derivatives which were synthesized *via* Claisen–Schmidt condensation and Algar–Flynn–Oyamada reaction, showing potent TNF-α inhibition. 5 – Fluoro – 3 – hydroxyl – 2 - (2, 4, 5-trimethoxyphenyl)-4H-chromen-4-one (Compound 27) **Fig. 9** with 81% TNF-α and 92% IL-6 inhibition at 10 μM was the most promising among all the derivatives. The 5-, 6-, and 7-positions are favourable sites for the higher potency. The compounds in the same series with -F at 5 and 7 positions or both, as well as -CF3 at 6-positions, exhibited the highest TNF-α and IL-6 inhibitory activity, as compared to the presence Cl, Br, CH_3, CN, and NO_2 substituents at the same positions **Fig. 9** demonstrated no TNF-α or IL-6 inhibitory activity [42]. Hilmy *et al.* synthesized Diaryl pyrrolopyrimidine and pyrrolothiazine derivatives as inhibitors of TNF-stimulated gene-14 (TSG-14), with (Compound 28) **Fig. 9** exhibiting the highest activity (80% TSG-14 inhibition), thus demonstrating its potential as an anti-inflammatory agent [43].

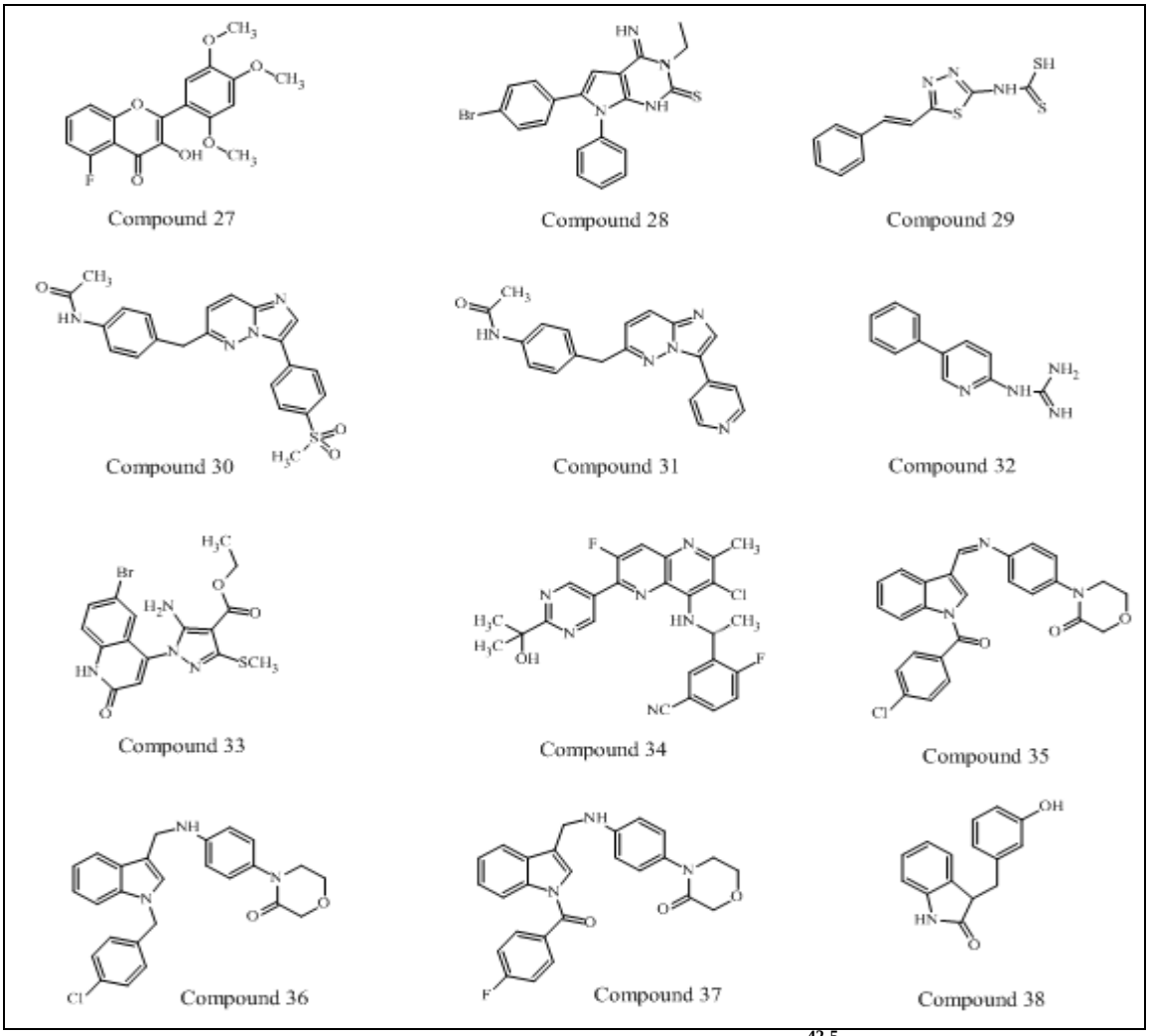

FIG. 9: REPORTED TNF-A INHIBITORS [42-5]

A study on new dithioic acid derivatives produced by the reaction of natural acids with thiosemicarbazide was carried out by Deepu *et al*., demonstrating significant anti-inflammatory activity through specific inhibition of TNF-α. Among the compounds tested, (Compound 23) **Fig.**

9 exhibited the highest *in-vitro* and *in-vivo* inhibition rates of 60.09% and 55.96%, respectively. The author highlighted the potential of these derivatives as effective anti-inflammatory agents by targeting TNF-α, a key cytokine in the inflammatory response [45]. Pandit *et al*. reported that the imidazo [1,2-b] pyridazine derivative (Compound 30) **Fig. 9** exhibited remarkable potency as a TNF-α production inhibitor, with an IC_{50}= 0.4 μM. This efficacy significantly surpasses that of conventional TNF-α inhibitors such as Rolipram, which requires a concentration of 300 μM to achieve 100% inhibition. Additionally, (Compound 31) **Fig. 9** also showed promising activity with an IC_{50} of 0.9 μM. These findings underscore the potential of imidazo[1,2-b] pyridazines as promising alternatives for treatment of inflammatory diseases, offering enhanced efficacy compared to existing therapeutic options [44].

Bollenbach *et al.* identified compound 4-phenylpyridin-2-yl-guanidine (Compound 32) **Fig. 9** as a potent inhibitor of TNF-α overproduction, exhibiting an IC_{50} of 1.2 μM. In models of acute lung inflammation and neuropathic pain, this compound and its rigid mimetic 2-amino dihydroquinazoline showed strong anti-inflammatory effects, indicating a potential substitute for conventional TNF-α inhibitors like etanercept and infliximab, which have a number of side effects and need to be carefully managed by the patient. The presence of a phenyl ring at position 4 of the pyridine nucleus was essential for the activity of (Compound 32). Shifting the phenyl ring to positions 3, 5, or 6 resulted in inactive compounds, indicating that the para position is crucial for maintaining the desired pharmacological effect [46].

Using TNF-α inhibition and caspase-3 tests, Aly *et al.* produced quinoline-2-one/pyrazole compounds and evaluated their anti-inflammatory properties. The derivative that demonstrated the strongest action against the most susceptible cell lines, leukaemia CCRF-CEM and MOLT-4, was Compound 33 **Fig. 9**. Its IC_{50} values were 1.35 μM and 2.42 μM for MOLT-4 and CCRF-CEM, respectively significantly reducing TNF-α levels with superior anti-inflammatory effects compared to the reference compound N-acetylcysteine [47].

In another study, Xiao *et al*. identified substituted 4-aminoquinolines and 4-aminonaphthyridines as TNF-α inhibitors by using scaffold hopping and structure-based drug discovery. By consolidating the trimer in an inactive configuration, the most potent compound, Compound 34 **Fig. 9,** demonstrated an IC_{50} of 41 nM in the HEK-Blue assay and successfully inhibited TNF-α/TNFR signalling [48]. When comparing these studies, Compound 33 demonstrated significant antioxidant and anti-inflammatory activities, whereas Compound 27 excelled in disrupting TNF-αsignalling via a novel allosteric mechanism. These findings collectively highlight the versatility of quinoline-based derivatives in modulating TNF-α activity [48, 49]. Similarly, Indole-based compounds have been gaining momentum as potential candidates in the treatment of rheumatoid arthritis (RA) because of their ability to target important inflammatory pathways. Indole analogues may have a strong inhibiting effect on tumour necrosis factor-alpha (TNF-α) [50, 51].

A cytokine responsible and active in the progression of RA, and inhibit other pro-inflammatory substances including interleukin-6 (IL-6) and nitric oxide (NO). Thus, not only inhibiting the inflammatory process through these indole structures, joint swelling as well as cartilage loss and also bone loss, which are the classic symptoms of RA, will also be addressed. Their ability to modulate the NF-κB signaling pathway also hints at a potential role in therapy, making the indole derivatives a good scaffold for the development of novel anti-rheumatoid arthritis drugs [50].

Singh *et al*. and Kaur *et al*. have both focused on rationally designing and synthesizing indole derivatives to target TNF-α, a key cytokine involved in inflammatory and tumour-related pathways. Singh *et al*. developed conjugates of N-substituted indole and aminophenylmorpholin-3-one, identifying (Compound 35) **Fig. 9** as the most potent, with a 71% reduction in TNF-α levels and 53% reduction in IL-6 in microglial cells. It also demonstrated strong inhibition of NO and MMP release, along with preventing NF-κB translocation. Similarly, the synthesized indole-morpholinone hybrids and identified Compound 36 & 37 **Fig. 9**, which inhibited TNF-α production by 75% at 1 μM

and displayed GI_{50} values as low as 0.15 μM in various tumour cell lines, indicating its dual anti-inflammatory and cytotoxic potential [51]. Kim *et al*. conducted a comprehensive study on the design, synthesis, and biological evaluation of 3-substituted-indolin-2-one derivatives **Fig. 9**, identifying their potential as anti-inflammatory agents. The studies utilize RAW264.7 murine macrophages to assess the biological activity of the synthesized compounds. Among the nineteen synthesized derivatives, 3-(3-hydroxyphenyl)-indolin-2-one (Compound 37) **Fig. 9** exhibited the highest anti-inflammatory activity, with an IC_{50} value demonstrating significant inhibition of nitric oxide production and pro-inflammatory cytokines in a concentration-dependent manner.

This compound effectively suppressed the generation of TNF-α and IL-6, also the mRNA expression of iNOS, indicating its potential as a therapeutic agent for inflammatory diseases [50]. Thalidomide [52, 53], ibuprofen [54], sinomenine [55], and tryptanthrin oxime [56], derivatives represent diverse pharmacophores with anti-inflammatory and immunomodulatory properties, targeting key mediators like TNF-α, IL-6, and IL-1β in rheumatoid arthritis (RA). By modulating pathways such as NF-κB, MAPK, and COX, these compounds reduce inflammation and alleviate RA symptoms. Thalidomide acts as an immunomodulator, ibuprofen inhibits prostaglandin synthesis, while sinomenine and tryptanthrin oxime derivatives showcase natural and synthetic pharmacophore diversity. Together, they emphasize the value of multi-pathway targeting in RA management and inspire novel therapeutic development [50-56].

Bruton's Tyrosine Kinase (BTK) Inhibition: Bruton's tyrosine kinase (BTK), also known as Bruton's agammaglobulinemia tyrosine kinase, is an important cytoplasmic non-receptor tyrosine kinase that plays a significant role in B cell development, differentiation, and signalling [57]. BTK is mostly expressed in hematopoietic cells, such as B lymphocytes, mast cells, and myeloid cells. It belongs to the Tec family of kinases, which also contains other kinases including ITK, BMX, and TEC [58]. Among its various isoforms, BTK-A is the most extensively studied and is characterized by its five distinct protein interaction domains: an N-terminal pleckstrin homology (PH) domain, a Tec homology (TH) domain, and Src homology (SH) domains (SH2 and SH3), along with a C-terminal kinase domain responsible for its enzymatic activity [59].

BTK is integral to the B-cell receptor (BCR) signalling pathway; upon BCR engagement with antigens, BTK undergoes phosphorylation by upstream kinases such as Lyn and Syk [60, 61]. This activation triggers phospholipase C-gamma (PLCγ), which causes the generation of second messengers that propagate crucial downstream signalling cascades, including those involving NF-κB and Akt pathway [61].

Given its central role in mediating B cell responses, BTK has emerged as a potential therapeutic target for diseases associated with B cell dysregulation, such as rheumatoid arthritis (RA) [62]. Initially investigated in the context of haematological malignancies, BTK inhibitors like ibrutinib have demonstrated efficacy in treating various B-cell cancers and are now being explored for their potential benefits in RA management [57-60].

The inhibition of BTK not only disrupts the survival and activation of autoreactive B cells but also offers a novel approach to modulating the inflammatory processes characteristic of RA. Additionally, BTK's expression in myeloid cells such as macrophages and neutrophils highlights its role in the inflammatory response seen in RA, as these cells contribute to cytokine production that exacerbates joint inflammation [59]. Research has shown that targeting BTK can effectively reduce disease severity in animal models of RA, indicating its multifaceted role in both B cell and innate immune responses [62].

Furthermore, ongoing clinical trials are investigating various selective BTK inhibitors beyond ibrutinib that may offer improved efficacy and safety profiles for RA patients [61, 62]. Some of them under pipeline are Compound 39 with 8.2 nM potency based on a FRET (Fluorescence resonance energy transfer) biochemical assay. It showed good potency against BTK at ambient bioscience screening done against more than 100 kinases. Compound 39 also exhibited inhibitory activity against Src family kinases [63].

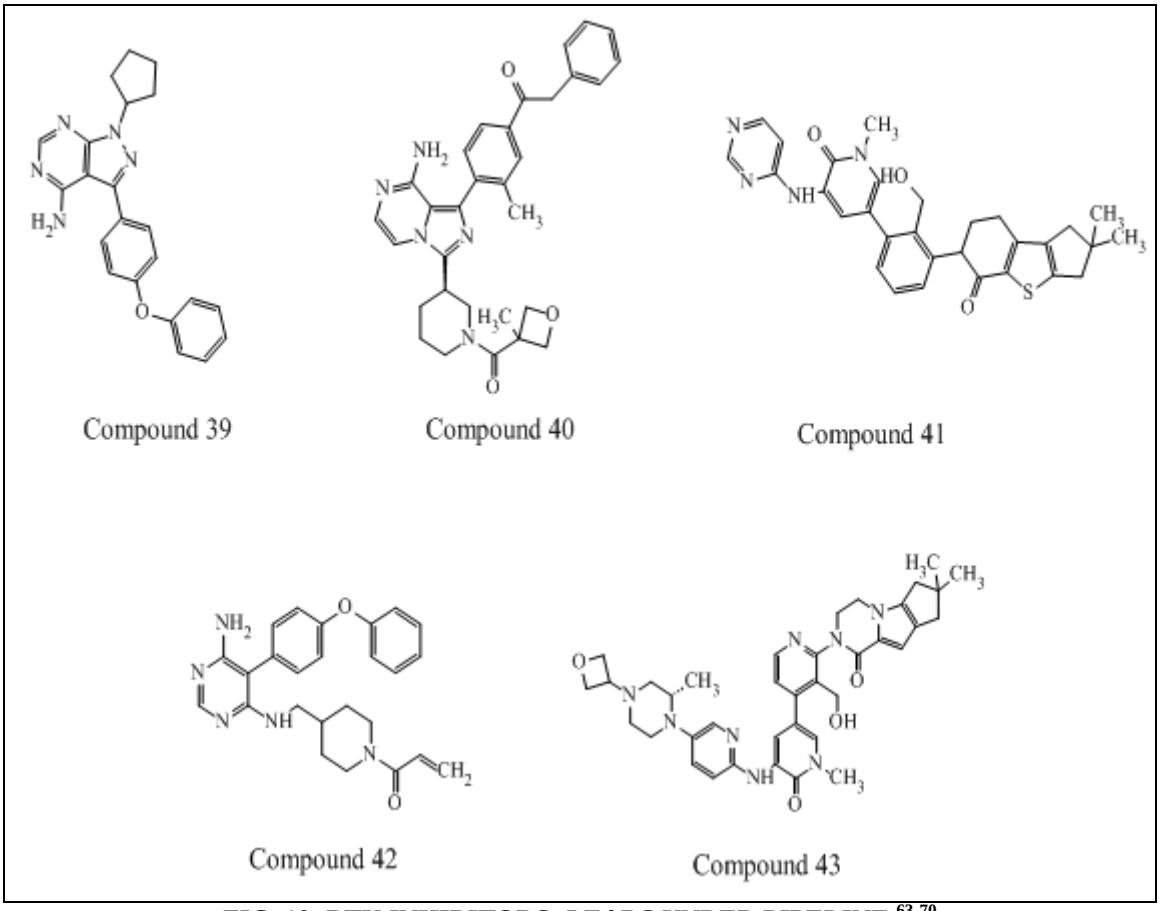

FIG. 10: BTK INHIBITORS- LEADS UNDER PIPELINE [63-70]

A series of 8-amino-imidazo [1,5-α] pyrazine scaffold (Compound 40) **Fig. 10** resulted in several promising analogues with excellent BTK inhibitory activity [61]. G-744 Compound 41 in **Fig. 10**. in animal studies was found to be highly potent, selective for BTK and metabolically stable with an IC_{50}:0.02nM [64]. Merck Group, Compound 42 (A18, M2951, IC_{50}:8.9nM) is a lead under phase IIb clinical trials, aimed to treat autoimmune diseases including RA. It has a great kinase selectivity profile and acceptable preclinical pharmacokinetic and pharmacodynamic profile [65].

Mostly all the structures consist of amino pyrimidine functionality **Fig. 10**. Additionally, Fenebrutinib (Compound 43), a second generation non covalent BTK inhibitor with amino pyridine scaffold is under phase II clinical trial. It is highly selective and well tolerated in phase I thereby encountering the issue of insufficient potency [66, 67]. BTK, a key RA regulator, is targeted by SOMCL-17-016 (Compound 44), a novel selective BTK inhibitor. In a mouse CIA model, SOMCL-17-016 (6.25–25 mg/kg) reduced arthritis severity and bone damage, outperforming ibrutinib and acalabrutinib. It inhibited B cell activation, RANKL expression, and osteoclast differentiation via RANK-BTK-PLCγ2-NFATc1 signalling. This dual action makes SOMCL-17-016 a promising RA treatment [68]. Poseltinib (HM71224) (Compound 45), a novel BTK inhibitor, irreversibly inhibits BTK (IC_{50}= 1.95 nM), suppresses cytokine production, and prevents osteoclast formation. In a mouse CIA model, it reduced arthritis severity and joint destruction, showing potential as a therapeutic for rheumatoid arthritis [69].

TAS5315 (Compound 46), a Bruton's tyrosine kinase inhibitor (IC_{50} = 0.85 nM), suppresses B-cell receptor signalling, macrophage cytokine production, and osteoclast activity. TAS5315 is a promising treatment for rheumatoid arthritis by increasing bone density and decreasing joint pathology in collagen-induced arthritis models [70]. Overall these chemical characteristics suggest that amino groups at ortho positions of nitrogen-containing heterocyclic scaffolds may be helpful to inhibit BTK associated with RA.

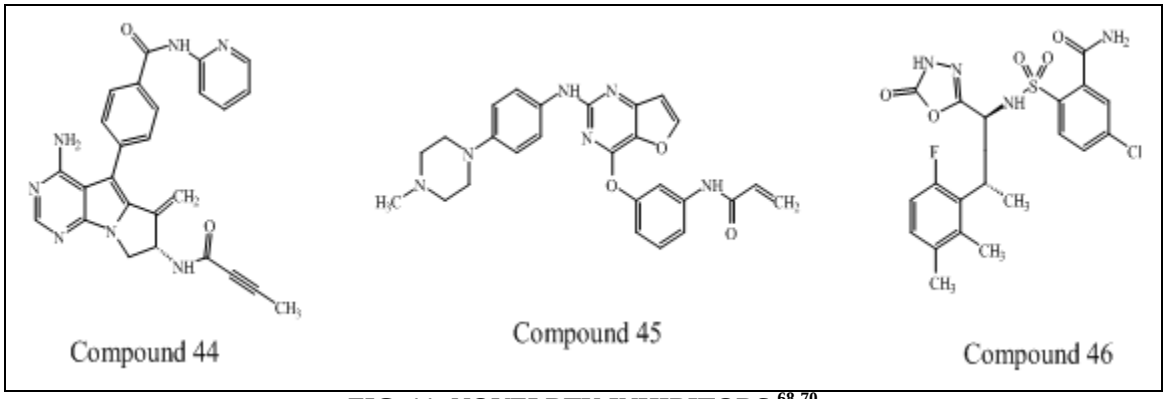

FIG. 11: NOVELBTK INHIBITORS [68-70]

Drugs under Clinical Investigation and Preclinical Trials [67-131]: The above indicated biological targets are being extensively explored by researchers and data for some of the drugs which are under clinical investigation and preclinical trials for the same have been compiled in **Table 1.**

TABLE 1: DRUGS UNDR CLINICAL INVESTIGATION AND PRECLINICAL TRIALS

Sr. no.	Drug Name	Type	Status	Reference
1	Ritlecitinib	JAK	Phase-II	71
2	Fostamatinib	JAK	Phase-III	67
3	Peresolimab	JAK	Phase-II	72
4	INCB18424	JAK	Phase-III	73, 74
5	TLL018	JAK	Preclinical trials	75, 76
6	Combination of Baricitinib and Methotrexate	JAK-	Phase-III	77
7	SHR-0302	JAK-1	Phase -III	78
8	CP-690,550	JAK-1	Phase-III	75, 79
9	Combination of baricitinib and adalimumab	JAK-1/2	Phase-III	77, 80, 81
10	VX-509	JAK-2	Phase II	67
11	CEP-33779	JAK-2	Preclinical trials	67
12	AC430	JAK-2	Phase-III	68
13	Ruxolitinib	JAK-2	Phase II	67, 78
14	CURCULIGOSIDE	JAK 1 and 3	Preclinical trials	75, 82
15	Ritlecitinib	JAK-3	Phase-II	70
16	R-348	JAK-3	Phase-I	83
17	Filgotinib, Methotrexate placebo	Pan JAK	Phase-III	79, 84
18	Delgocitinib	Pan- JAK	Phase III	85
19	Ozoralizumab	TNF	Phase-II	86
20	Secukinumab	TNF	Phase-III	87, 88
21	ABBV-154	TNF	Phase-I	89
22	Combination of golimumb and Methotrexate	TNF	Phase-III	90-92
23	Combination of infliximab plus Methotrexate	TNF	Phase-III	93-96
24	Combination of Etanercept and Methotrexate	TNF	Phase-II	97-100
25	Amino-triazine analogues	BTK	Preclinical trials	101
26	CC-292	BTK	Phase-I	102, 103
27	HM71224	BTK	Clinical Trial	104
28	CGI-1746	BTK	Preclinical trials	105
29	RN-486	BTK	Preclinical trials	105-107
30	PRN-1008	BTK	Phase-II	108
31	GDC-0834	BTK	Phase-I	106, 107, 109
32	Tirabrutinib	BTK	Phase-I	110
33	Spebrutinib	BTK	Preclinical trials	111
34	CNX-774	BTK	Preclinical trials	112
35	Imidazoquinoxaline	BTK	Preclinical trials	112, 113
36	Acalabrutinib	BTK	Phase-II	89, 114
37	SOMCL-17-016	BTK	Preclinical trials	115
38	Branebrutinib	BTK	Phase-II	116
39	BMS-986142	BTK	Phase-II	117, 118

40	Ibrutinib	BTK	Phase-II	119, 120
41	Evobrutinib/ M2951	BTK	Phase-II	121, 122
42	Remibrutinib / LOU064	BTK	Phase-II	123
43	TAK-020	BTK	Phase-I	124
44	ABBV-105/Elsubrutinib	BTK	Phase-II	125
45	Fenebrutinib / GDC0853/RG7845	BTK	Phase-II	126
46	Orelabrutinib (ICP-022)	BTK	Phase-I	127
47	TAS5315	BTK	Phase-II	128, 129
48	Namilumab	Anti-PD-1 monoclonal antibody	Phase III	130
49	RC18	TACl – Fc fusion protein targeting B – cells	Phase III	131

Emerging Alternative Therapies for RA: The unique capacity of mesenchymal stem cells (MSCs) to alter the immune system, the stem cell therapy is currently being studied as a potential treatment option for individuals with RA DMARDs on long exposure possess adverse effect of systemic weakening of the immune system[131, 132]. In a study conducted by Huang *et al.* in 2019, which involved 64 RA patients, discovered that mesenchymal stem cell therapy is a safe treatment option [133]. MSCs are differentiating cells capable of forming cartilage, bone, and adipose tissue. Preclinical studies have also shown a positive result in the ability of MSCs to repair tissues, tissue regeneration and its immunomodulatory effects. They play a significant role in the suppression of the immune system by inhibiting the production of inflammatory cytokines [131].

MSCs convert T cells into regulatory T cells, or Tregs, which are crucial for preserving tolerance and averting RA. They also result in a decrease in Th17/Th1 cells, a reduction in the immunological response to B cells, an increase in IL-10 release, and an increase in Treg cell formation [134]. Ongoing research is evaluating mesenchymal stem cells for reducing inflammation, repairing joint damage, and slowing disease progression. Mesenchymal stem cell (MSC) therapy is being explored for its potential to repair damaged joints and reduce inflammation [131-135]. The DEN-181 Vaccine is undergoing the first human trials with an aim to use it to reprogram immune responses in RA patients [136]. Neurostimulation devices, such as vagus nerve stimulators are under investigation for managing RA by modulating immune system activity. Vagus Nerve Stimulation (VNS) experimental trials for VNS have shown promise in reducing RA symptoms through neurostimulation [136, 137]. Monoclonal antibody, Olokizumab is under Phase III trials, Its target interleukin-6 (IL-6); superior to placebo and comparable to adalimumab (Humira) in trials [138, 139].

CONCLUSION: The therapeutic landscape for rheumatoid arthritis has evolved significantly, transitioning from conventional DMARDs to more targeted approaches involving biological DMARDs. While TNF-α inhibitors like Etanercept and Infliximab remain the most widely prescribed, the increasing focus on Janus kinase (JAK) and Bruton's Tyrosine Kinase (BTK) inhibitors highlights a shift toward precision medicine in RA. On structural investigation of the biological DMARDs explored, many of them possess pyrimidine scaffold which exist as fused ring system with different heterocycles such as pyrrole, imidazole, pyrazole, amino substituted pyrimidinering has been linked to rings like aryl, heteroaryl, sulfonamido groups. All the above findings, indicate potential role of pyrimidine scaffold in drug design. Despite the efficacy of these agents, unmet clinical needs persist, especially in those patients who don't react well to current treatments.

Emerging strategies such as mesenchymal stem cell (MSC) therapy offer a novel paradigm by targeting tissue regeneration and immune modulation rather than solely symptom management. Early clinical trials of the DEN-181 vaccine and vagus nerve stimulation devices indicate potential in reshaping immune responses and reducing systemic inflammation in RA. Among biological targets, BTK inhibitors are gaining attention, with promising preclinical and clinical candidates showing high selectivity and potency. The current trajectory suggests a future where combination therapies integrating bDMARDs, stem cell therapies, and novel immunomodulatory

approaches could provide a holistic and personalized solution for RA management. Further research and clinical validation are essential to translate these innovations into effective, widely accessible treatments.

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REFERENCES:

1. Conforti A, Di Cola I, Pavlych V, Ruscitti P, Berardicurti O, Ursini F, Giacomelli R and Cipriani P: Beyond the joints, the extra articular manifestations in rheumatoid arthritis. Autoimmunity Reviews 2021; 20: 102735. https://doi.org/10.1016/j.autrev.2020.102735
2. Smolen JS, Aletaha D and McInnes IB: Rheumatoid arthritis. The Lancet 2023; 388: 2023. https://doi.org/10.1016/S0140-6736(16)30173-8
3. Hsieh PH, Wu O, Geue C, McIntosh E, McInnes IB and Siebert S: Economic burden of rheumatoid arthritis: a systematic review of literature in biologic era. Annals of the Rheumatic Diseases 2020; 79: 771 777. https://doi.org/10.1136/annrheumdis-2019-216243
4. Global Health Metrics: Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet 2020; 396: 1204. https://doi.org/10.1016/S0140-6736(20)30925-9
5. Cieza A: Global estimates of the need for rehabilitation based on the Global Burden of Disease Study 2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet 2020; 396: 2006. https://doi.org/10.1016/S0140-6736(20)32340-0
6. Collaborators RA: Global, regional, and national burden of rheumatoid arthritis, 1990 2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. The Lancet Rheumatology 2023; 5. https://doi.org/10.1016/S2665-9913(23)00211-4
7. Radu AF and Bungau SG: Management of rheumatoid arthritis: an overview. Cells 2021; 10: 2857. https://doi.org/10.3390/cells10112857
8. Rajdan, Neeraj, Bhavana Srivastava and Kunal Sharma: Rheumatoid arthritis: treatments available at present. Nanotherapeutics for Inflammatory Arthritis. CRC Press 2024: 243-295.
9. Liang HY, Yin HX, Li SF, Chen Y, Zhao YJ, Hu W and Zhou RP: Calcium permeable channels cooperation for rheumatoid arthritis: therapeutic opportunities. Biomolecules 2022; 12: 1383. https://doi.org/10.3390/biom12101383
10. Bellomo A, Gentek R, Golub R and Bajénoff M: Macrophage fibroblast circuits in the spleen. Immunological Reviews 2021; 302: 104 125. https://doi.org/10.1111/imr.12979
11. Khan SA and Ilies MA: The Phospholipase A2 Superfamily: Structure, Isozymes, Catalysis, Physiologic and Pathologic Roles. International Journal of Molecular Sciences 2023; 24:1353. https://doi.org/10.3390/ijms24021353
12. Chen C, Guan J, Gu X, Chu Q and Zhu H: Prostaglandin E2 and Receptors: Insight Into Tumorigenesis, Tumor Progression, and Treatment of Hepatocellular Carcinoma. Frontiers in Cell and Developmental Biology 2022; 10: 834859. https://doi.org/10.3389/fcell.2022.834859
13. Lu Z, Xiao P, Liu S, Huang C, Li W, Mao Y, Xu Y and Tian Y: Osteoimmunology: crosstalk between T cells and osteoclasts in osteoporosis. Clinical Reviews in Allergy & Immunology 2025; 68: 41. https://doi.org/10.1007/s12016-025-09046-1
14. Nicolle A, Zhang Y and Belguise K: The Emerging Function of PKCθ in Cancer. Biomolecules 2021; 11: 221. https://doi.org/10.3390/biom11020221
15. Li Y, Ye R, Dai H, Lin J, Cheng Y, Zhou Y and Lu Y: Exploring TNFR1: from discovery to targeted therapy development. Journal of Translational Medicine 2025; 23: 71. https://doi.org/10.1186/s12967-025-06122-0
16. Payal Ganguly, Macleod T, Wong C, Harland M and McGonagle D: Revisiting p38 Mitogen Activated Protein Kinases (MAPK) in Inflammatory Arthritis: the emergence of MAPK activated protein kinase inhibitors (MK2i). Pharmaceuticals 2023; 16: 1286. https://doi.org/10.3390/ph16091286
17. Chen X, Li X, Xu X, Li L, Liang N, Zhang L, Lv J, Wu YC and Yin H: Ferroptosis and cardiovascular disease: role of free radical induced lipid peroxidation. Free Radical Research 2021; 55: 405 415. https://doi.org/10.1080/10715762.2021.1876856
18. Doan T, Massarotti E: Rheumatoid arthritis: an overview of new and emerging therapies. Journal of Clinical Pharmacology 2005; 45:751. https://doi.org/10.1177/0091270005277938
19. Deshmukh R: Rheumatoid arthritis: pathophysiology, current therapeutic strategies and recent advances in targeted drug delivery system. Materials Today Communications 2023; 35:105877. https://doi.org/10.1016/j.mtcomm.2023.105877
20. Kuriachan A, Thomas RR and Sukanya R: Aqua mediated multicomponent synthesis of N, O heterocycles and biological activity of fused isoxazole derivatives. Five Membered Bioactive N and O Heterocycles 2025; 495 536. https://doi.org/10.4018/979-8-3693-7267-8.ch012
21. Ding Q, Hu W, Wang R, Yang Q, Zhu YZ and Mao JC: Signaling pathways in rheumatoid arthritis: implications for targeted therapy. Signal Transduction and Targeted Therapy 2023; 8: 68. https://doi.org/10.1038/s41392-023-01331-9
22. Mysler E, Caubet M and Lizarraga A: Current and emerging DMARDs for the treatment of rheumatoid arthritis. Open Access Rheumatology: Research and Reviews 2021; 13: 139–152. https://doi.org/10.2147/OARRR.S282627
23. Tanaka Y: Recent progress in treatments of rheumatoid arthritis: an overview of developments in biologics and small molecules, and remaining unmet needs. Rheumatology 2021; 60(6): 12–20. https://doi.org/10.1093/rheumatology/keab609
24. Chen C, Sun L, Zhang D and Zhang T: A highly selective JAK3 inhibitor developed for treating rheumatoid arthritis by suppressing γc cytokine–related JAK STAT signaling. Science Advances 2022; 8-4363. https://doi.org/10.1126/sciadv.abo4363
25. Rehman A, Rehman MU and Khan MS: Involvement and therapeutic implication of JAK STAT pathway in cancer. Cell Signaling Pathways and Their Therapeutic Implication in Cancers 2025; https://doi.org/10.1007/978-981-96-2763-9_8
26. Mueller AL, Payandeh Z, Mohammadkhani N, Mubarak SMH, Zakeri A, Alagheband Bahrami A, Brockmueller A

and Shakibaei M: Recent advances in understanding the pathogenesis of rheumatoid arthritis: new treatment strategies. Cells 2021; 10: 3017.

27. Alanazi F, Abdulaziz S, Alghanim K, Alhamzi H, Alrayes H: Diagnostic delay in rheumatoid arthritis patients: a multi centric study conducted in Saudi Arabia. Annals of Rheumatology and Autoimmunity 2025; 56-60. https://doi.org/10.4103/ara.ara_11_23
28. Shawky AM, Almalki FA, Abdalla AN, Abdelazeem AH and Gouda AM: A comprehensive overview of globally approved JAK inhibitors. Pharmaceutics 2022; 14:1001. https://doi.org/10.3390/pharmaceutics14051001
29. Tanaka Y, Izutsu H: Peficitinib for the treatment of rheumatoid arthritis: an overview from clinical Expert Opinion on Pharmacotherapy 2020; 21:1015. https://doi.org/10.1080/14656566.2020.1739649
30. Aishwarya Bharathi HM and Dubey S: Fundamental chemistry of N heterocycles: pyrrole and pyrazole chemistry, imidazole chemistry, triazole chemistry advances in heterocyclic ring systems. Paving the Path to Discoveries and Unlocking the Secrets of N Heterocycles 2024; 64.
31. Gehringer M, Pfaffenrot E, Bauer S, Laufer SA: Design and synthesis of tricyclic JAK3 inhibitors with picomolar affinities as novel molecular probes. ChemMedChem 2014; 9:277. https://doi.org/10.1002/cmdc.201300520
32. Kaur M, Singh M, Silakari O: Oxindole-based SYK and JAK3 dual inhibitors for rheumatoid arthritis: designing, synthesis and biological evaluation. Future Medicinal Chemistry 2017; 9:1193. https://doi.org/10.4155/fmc-2017-0037
33. He L, Pei H, Lan T, Tang M, Zhang C, Chen L: Full paper. Archiv der Pharmazie 2017; 350:1. https://doi.org/10.1002/ardp.201700194
34. He L, Shao M, Wang T, Lan T, Zhang C and Chen L: Design, synthesis, and SAR study of highly potent, selective, irreversible covalent JAK3 inhibitors. Molecular Diversity 2018; 22:817. https://doi.org/10.1007/s11030-017-9803-2
35. Fensome A: Dual inhibition of TYK2 and JAK1 for the treatment of autoimmune diseases: discovery of ((S)-2,2-difluorocyclopropyl)((1R,5S)-3-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone (PF-06700841). Journal of Medicinal Chemistry 2018; 61:8597. https://doi.org/10.1021/acs.jmedchem.8b00917
36. Shu L: Design, synthesis, and pharmacological evaluation of 4- or 6-phenyl-pyrimidine derivatives as novel and selective Janus kinase 3 inhibitors. European Journal of Medicinal Chemistry 2020; 191:112148. https://doi.org/10.1016/j.ejmech.2020.112148
37. Covington M: Preclinical characterization of itacitinib (INCB039110), a novel selective inhibitor of JAK1, for the treatment of inflammatory diseases. European Journal of Pharmacology 2020; 885: 173505. https://doi.org/10.1016/j.ejphar.2020.173505
38. Fatima F, Chourasiya NK, Mishra M, Kori S, Pathak S, Das R, Kashaw V, Iyer AK and Kashaw SK: Curcumin and its derivatives targeting multiple signaling pathways to elicit anticancer activity: a comprehensive perspective. Current Medicinal Chemistry 2024; 31: 3668 3714. https://doi.org/10.2174/0929867330666230522144312
39. Deshmukh R: Rheumatoid arthritis: pathophysiology, current therapeutic strategies and recent advances in targeted drug delivery system. Materials Today Communications 2023; 35: 105877. https://doi.org/10.1016/j.mtcomm.2023.105877
40. Lakhmiri R, Cherrah Y and Serragui S: Tumor Necrosis Factor α (TNF α) antagonists used in chronic inflammatory rheumatic diseases: risks and their minimization measures. Current Drug Safety 2024; 19: 431 443. https://doi.org/10.2174/0115748863274863231222023853
41. Riaz M, Rasool G, Yousaf R, Fatima H, Munir N and Ejaz H: Anti Rheumatic potential of biological DMARDs and protagonistic role of bio markers in early detection and management of rheumatoid arthritis. Innate Immunity 2025; https://doi.org/10.1177/17534259251324820
42. Hatnapure GD, Keche AP, Rodge AH: Trimethoxyflavonol derivatives as anti-inflammatory and antimicrobial agents. Medicinal Chemistry Research 2013; 22:5240. https://doi.org/10.1007/s00044-013-0651-z
43. Hilmy KM, Soliman DH, Shahin EB, El-Deeb HS, El-Kousy SM: Design, synthesis and evaluation of novel diaryl pyrrolopyrimidine and pyrrolothiazine derivatives as inhibitors of tumor necrosis factor stimulated gene-14 (TSG-14) production. European Journal of Medicinal Chemistry 2014; 78:419. https://doi.org/10.1016/j.ejmech.2014.03.068
44. Pandit SS, Kulkarni MR, Ghosh U, Pandit YB, Lad NP: Synthesis and biological evaluation of imidazo[1,2-b]pyridazines as inhibitors of TNF-α production. Molecular Diversity 2018; 22:545. https://doi.org/10.1007/s11030-017-9798-8
45. Kp D, Thomas B and Harindran J: Design, synthesis and evaluation of specific TNF-α inhibitory novel dithioic acid derivative from natural acids as anti-inflammatory agents. International Journal of Pharmacy and Chemistry 2016; 6:25. https://doi.org/10.7439/ijpc
46. Bollenbach M: Phenylpyridine-2-ylguanidines and rigid mimetics as novel inhibitors of TNF-α overproduction: beneficial action in models of neuropathic pain and acute lung inflammation. European Journal of Medicinal Chemistry 2018; 147:420. https://doi.org/10.1016/j.ejmech.2018.01.049
47. Ahmed AE, Thabet K, El-Reedy AAM, Alan B and Bräse S: New quinoline-2-one/pyrazole derivatives: design, synthesis, molecular docking, anti-apoptotic evaluation, and caspase-3 inhibition assay. Bioorganic Chemistry 2019; 90: 103348. https://doi.org/10.1016/j.bioorg.2019.103348
48. Xiao H: Biologic-like *in-vivo* efficacy with small molecule inhibitors of TNF-α identified using scaffold hopping and structure-based drug design approaches. Journal of Medicinal Chemistry 2021; 64: 13578. https://doi.org/10.1021/acs.jmedchem.0c01732
49. Kaur B, Mishra S, Kaur R, Kalotra S and Singh P: Rationally designed TNF-α inhibitors: identification of promising cytotoxic agents. Bioorganic and Medicinal Chemistry Letters 2021; 41: 127982. https://doi.org/10.1016/j.bmcl.2021.127982
50. Kim SJ, Lee SH, Lee H, Shin MS and Lee JW: Design, synthesis, and biological evaluation of 3-substituted-indolin-2-one derivatives as potent anti-inflammatory agents. International Journal of Molecular Sciences 2023; 24:2066. https://doi.org/10.3390/ijms24032066
51. Singh P, Kaur S, Sharma A, Kaur G and Bhatti R: TNF-α and IL-6 inhibitors: conjugates of N-substituted indole and aminophenylmorpholin-3-one as anti-inflammatory agents. European Journal of Medicinal Chemistry 2017; 139: 471. https://doi.org/10.1016/j.ejmech.2017.09.003
52. Shivaleela B, Srushti SC, Shreedevi SJ and Babu RL: Thalidomide-based inhibitor for TNF-α: designing and *in-silico* evaluation. Future Journal of Pharmaceutical

Sciences 2022; 8. https://doi.org/10.1186/s43094-021-00393-2

53. Cordovil K and Hada M: Prevention with Symbiosis, and Treatment with Thalidomide, Celecoxib, and Valproic Acid for Rheumatoid Arthritis. American Journal of Biomedical and Life Sciences 2022; 146-154. https://doi.org/10.11648/j.ajbls.20221005.13
54. Study H: Design and synthesis of novel ibuprofen derivatives as selective COX-2 inhibitors and potential anti-inflammatory agents: evaluation of PGE_2, TNF-α, IL-6 and histopathological study. Current Medicinal Chemistry 2022; 29: 427. https://doi.org/10.2174/1573406417666210809162636
55. Gao F: Sinomenine derivatives as anti-inflammatory agents. RSC Advances 2022; 12: 30001. https://doi.org/10.1039/d2ra05558a
56. Schepetkin IA: Design, synthesis and biological evaluation of novel O-substituted tryptanthrin oxime derivatives as c-Jun N-terminal kinase inhibitors. Frontiers in Pharmacology 2022; 13: 958687. https://doi.org/10.3389/fphar.2022.958687
57. De Bondt M, Beirnaert C, Vandecasteele M, Dendooven A, Elewaut D and Van Calenbergh S: Inhibitors of Bruton's tyrosine kinase as emerging therapeutic strategy in autoimmune diseases. Autoimmunity Reviews 2024; 23: 103532. https://doi.org/10.1016/j.autrev.2024.103532
58. Yin Z, Zou Y, Wang D, Li Y, Zhao Z, Liang X, Li J, Zhang C and Zhang Y: Regulation of the Tec family of non receptor tyrosine kinases in cardiovascular disease. Cell Death Discovery 2022; 8: 119. https://doi.org/10.1038/s41420-022-00927-4
59. Li W: Bruton's tyrosine kinase inhibitors with distinct binding modes reveal differential functional impact on B-cell receptor signaling. Molecular Cancer Therapeutics 2024; 23: 35. https://doi.org/10.1158/1535-7163.MCT-22-0642
60. Contentti EC and Correale J: Bruton's tyrosine kinase inhibitors: a promising emerging treatment option for multiple sclerosis. Expert Opinion on Emerging Drugs 2020; 25: 377. https://doi.org/10.1080/14728214.2020.1822817
61. Wang X, Kokabee L, Kokabee M and Conklin DS: Bruton's tyrosine kinase and its isoforms in cancer. Frontiers in Cell and Developmental Biology 2021; 9: 668996. https://doi.org/10.3389/fcell.2021.668996
62. Paliwal S, Bawa S, Shalmali N and Tonk RK: Therapeutic potential and recent progression of BTK inhibitors against rheumatoid arthritis. Chemical Biology & Drug Design 2024; 103: 14582. https://doi.org/10.1111/cbdd.14582
63. Liu J: Inhibitors for the treatment of rheumatoid arthritis. ACS Medicinal Chemistry Letters 2015; 6:736. https://doi.org/10.1021/acsmedchemlett.5b00463
64. Caldwell RD: Discovery of Evobrutinib: an oral, potent, and highly selective, covalent Bruton's tyrosine kinase (BTK) inhibitor for the treatment of immunological diseases. Journal of Medicinal Chemistry 2019; 62: 7643. https://doi.org/10.1021/acs.jmedchem.9b00794
65. Cohen S: Fenebrutinib versus placebo or adalimumab in rheumatoid arthritis: a randomized, double-blind, phase II trial. Arthritis & Rheumatology 2020; 72: 1435. https://doi.org/10.1002/art.41275
66. Zhang D, Gong H and Meng F: Recent advances in BTK inhibitors for the treatment of inflammatory and autoimmune diseases. Molecules 2021; 26: 4907. https://doi.org/10.3390/molecules26164907
67. Tanaka Y, Millson D, Iwata S and Nakayamada S: Safety and efficacy of fostamatinib in rheumatoid arthritis patients with an inadequate response to methotrexate in phase II OSKIRA-ASIA-1 and OSKIRA-ASIA-1X study. Rheumatology (Oxford, England) 2021; 60: 2884–2895. https://doi.org/10.1093/rheumatology/keaa732
68. Lomares Manzano I, Jimenez Pichardo L and Gomez Sayago L: Biologic agents in rheumatological diseases: impact of 'treat to target' in clinical practice. European Journal of Hospital Pharmacy 2022; 29: 61–62. https://doi.org/10.1136/ejhpharm-2022-eahp.130
69. Ge X: Mass balance study of [(14)C]SHR0302, a selective and potent JAK1 inhibitor in humans. Xenobiotica 2023; 53: 69. https://doi.org/10.1080/00498254.2023.2176267
70. Robinson MF, Damjanov N, Stamenkovic B, Radunovic G, Kivitz A, Cox L, Manukyan Z, Banfield C, Saunders M, Chandra D, Vincent MS, Mancuso J, Peeva E and Beebe JS: Efficacy and safety of PF-06651600 (Ritlecitinib), a novel JAK3/TEC inhibitor, in patients with moderate-to-severe rheumatoid arthritis and an inadequate response to methotrexate. Arthritis & Rheumatology (Hoboken, N.J.) 2020; 72: 1621–1631. https://doi.org/10.1002/art.41316
71. Tanaka Y, Luo Y, O'Shea JJ and Nakayamada S: Janus kinase-targeting therapies in rheumatology: a mechanisms-based approach. Nature Reviews Rheumatology 2022; 18: 133. https://doi.org/10.1038/s41584-021-00726-8
72. Tuttle J, Drescher E, Simón-Campos JA, Emery P, Greenwald M, Kivitz A, Rha H, Yachi P, Kiley C and Nirula A: A phase 2 trial of peresolimab for adults with rheumatoid arthritis. The New England Journal of Medicine 2023; 388: 1853–1862. https://doi.org/10.1056/NEJMoa2209856
73. Kivitz A, Wells AF, Vargas JI, Baraf HSB, Rischmueller M, Klaff J, Khan N, Li Y, Carter K, Friedman A and Durez P: Long-term efficacy and safety of upadacitinib in patients with rheumatoid arthritis: final results from the BALANCE-EXTEND open-label extension study. Rheumatology and Therapy 2023; 10: 901–915. https://doi.org/10.1007/s40744-023-00557-x
74. Jiang P, Wei K, Zhao J, Jin Y, Chang C, Zhang R and He D: Trends of treatment development in rheumatoid arthritis: promise, progress, and challenges. Preprints 2022; 4: 1. https://doi.org/10.20944/preprints202203.0071.v2
75. Han J, Wan M, Ma Z, Hu C and Yi H: Prediction of targets of curculigoside A in osteoporosis and rheumatoid arthritis using network pharmacology and experimental verification. Drug Design, Development and Therapy 2020; 14: 5235–5250. https://doi.org/10.2147/DDDT.S282112
76. Dermatology B: Safety and efficacy of selective TYK2/JAK1 inhibitor, TLL-018, in moderate-to-severe plaque psoriasis. Journal of the American Academy of Dermatology 2024; 91: 306. https://doi.org/10.1016/j.jaad.2024.07.1219
77. Caporali R, Taylor PC, Aletaha D, Sanmartí R, Takeuchi T, Mo D, Haladyj E, Bello N, Zaremba-Pechmann L, Fang Y and Dougados M: Efficacy of baricitinib in patients with moderate-to-severe rheumatoid arthritis up to 6.5 years of treatment: results of a long-term study. Rheumatology 2024; 63: 2799–2809. https://doi.org/10.1093/rheumatology/keae012
78. Zeng X, Liu J and Jiang Y: A multicenter, randomized, placebo-controlled, double-blind, phase 3 study of SHR0302, a selective Janus kinase 1 inhibitor, in patients with active rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs. Annals of the Rheumatic Diseases

2024.https://doi.org/10.1136/annrheumdis-2024-eular.1908
79. Kim ES and Keam SJ: Filgotinib in rheumatoid arthritis: a profile of its use. Clinical Drug Investigation 2021; 41: 741. https://doi.org/10.1007/s40261-021-01055-0
80. Taylor PC, Alten R, Álvaro Gracia JM, Kaneko Y, Walls C, Quebe A, Jia B, Bello N, Ross Terres J and Fleischmann R: Achieving pain control in early rheumatoid arthritis with baricitinib monotherapy or in combination with methotrexate versus methotrexate monotherapy. RMD Open 2022; 8: 001994. https://doi.org/10.1136/rmdopen-2021-001994
81. Asai S, Takahashi N and Terabe K: Clinical effectiveness of baricitinib and abatacept in patients with rheumatoid arthritis. International Journal of Rheumatic Diseases 2024; 27: 15414. https://doi.org/10.1111/1756-185X.15414
82. Han J, Wan M, Ma Z, Hu C and Yi H: Prediction of targets of curculigoside A in osteoporosis and rheumatoid arthritis using network pharmacology and experimental verification. Drug Design, Development and Therapy 2020; 14: 2821. https://doi.org/10.2147/DDDT.S282112
83. Bajkin I, Golubović S, Ičin T, Stepanović K and Ilić T: Can propylthiouracil induce autoimmune-related immunotoxicity? Vojnosanitetski pregled 2022; 79: 1162–1167. https://doi.org/10.2298/VSP210429067B
84. Combe B: Filgotinib versus placebo or adalimumab in patients with rheumatoid arthritis and inadequate response to methotrexate: a phase III randomised clinical trial. Annals of the Rheumatic Diseases 2021; 80: 848. https://doi.org/10.1136/annrheumdis-2020-219214
85. Potlabathini T, Pothacamuri MA, Bandi VV and Anjum M: FDA-approved Janus kinase-signal transducer and activator of transcription (JAK-STAT) inhibitors for managing rheumatoid arthritis: a narrative review of the literature. Cureus 2024; 16: 59978. https://doi.org/10.7759/cureus.59978
86. Tanaka Y: Ozoralizumab: first Nanobody® therapeutic for rheumatoid arthritis. Expert Opinion on Biological Therapy 2023; 23: 579–587. https://doi.org/10.1080/14712598.2023.2231344
87. Hauer L, Moztarzadeh O, Baghalipour N and Gencur J: Secukinumab causing medication-related osteonecrosis of the jaw, in a patient diagnosed with psoriasis and rheumatoid arthritis. Psoriasis: Targets and Therapy 2024; 14: 115–120. https://doi.org/10.2147/PTT.S490982
88. Gottlieb AB, Deodhar A, McInnes IB, Baraliakos X, Reich K, Schreiber S, Bao W, Marfo K, Richards HB, Pricop L, Shete A, Trivedi V, Keefe D, Papavassilis CC, Jagiello P, Papanastasiou P, Mease PJ and Lebwohl M: Long-term safety of secukinumab over five years in patients with moderate-to-severe plaque psoriasis, psoriatic arthritis and ankylosing spondylitis: update on integrated pooled clinical trial and post-marketing surveillance data. Acta Dermato-Venereologica 2022; 102: 00698.
89. Hobson AD, Xu J, Welch DS, Marvin CC, McPherson MJ, Gates B and Liao X: Discovery of ABBV-154, an anti-TNF glucocorticoid receptor modulator immunology antibody-drug conjugate (iADC). Journal of Medicinal Chemistry 2023; 66: 12544–12558. https://doi.org/10.1021/acs.jmedchem.3c01174
90. Naniwa T and Kajiura M: Long-term effectiveness and safety of methotrexate–tacrolimus combination therapy versus methotrexate monotherapy in reducing rheumatoid arthritis flares after TNF inhibitor discontinuation: a retrospective cohort study. BMC Rheumatology 2025; 9: 39. https://doi.org/10.1186/s41927-025-00489-9
91. Broadwell A, Schechtman J and Conaway D: Effectiveness and safety of intravenous golimumab with and without concomitant methotrexate in patients with rheumatoid arthritis in the prospective, noninterventional AWARE study. BMC Rheumatology 2023; 7:5. https://doi.org/10.1186/s41927-023-00329-8
92. Husni ME, Deodhar A and Schwartzman S: Pooled safety results across phase 3 randomized trials of intravenous golimumab in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. Arthritis Research & Therapy 2022; 24:73. https://doi.org/10.1186/s13075-022-02753-6
93. Sullivan MM, Pham MM and Marks LA: Intra-articular therapy with methotrexate or tumor necrosis factor inhibitors in rheumatoid arthritis: a systematic review. BMC Musculoskeletal Disorders 2021; 22:792. https://doi.org/10.1186/s12891-021-04651-5
94. Imam AA: Anti-TNF alpha and risk of lymphoma in rheumatoid arthritis: a systematic review and meta-analysis. Medicina (Kaunas) 2024; 60: 1156. https://doi.org/10.3390/medicina60071156
95. Venetsanopoulou AI, Voulgari PV and Drosos AA: Optimizing withdrawal strategies for anti-TNF-α therapies in rheumatoid arthritis. Expert Opinion on Biological Therapy 2024; 24: 815–825. https://doi.org/10.1080/14712598.2024.2384000
96. Patel KHK, Jones TN, Sattler S, Mason JC and Ng FS: Proarrhythmic electrophysiological and structural remodeling in rheumatoid arthritis. American Journal of Physiology-Heart and Circulatory Physiology 2020; 319: 1008. https://doi.org/10.1152/ajpheart.00401.2020
97. Curtis JR, Emery P, Karis E, Haraoui B, Bykerk V, Yen PK, Kricorian G, Chung JB: Etanercept or methotrexate withdrawal in rheumatoid arthritis patients in sustained remission. Arthritis & Rheumatology 2021; 73:759–768. https://doi.org/10.1002/art.41589
98. Strusberg I, Mysler E, Citera G, Siri D, de los Ángeles Correa M, Lazaro MA, Pardo Hidalgo R, Spindler A, Tate P, Venarotti H, Velasco Zamora J, Klimovsky E, Federico A, Scheines E, Gonzalez E, Cordeiro L and Lago N: Efficacy, safety, and immunogenicity of biosimilar etanercept (Enerceptan) versus its original form in combination with methotrexate in patients with rheumatoid arthritis: a randomized, multicenter, evaluator-blinded, noninferiority study. Journal of Clinical Rheumatology 2021; 27(Suppl 6): 173–179. https://doi.org/10.1097/RHU.0000000000001616
99. Mulder MLM, Vriezekolk JE, van Hal TW, Nieboer LM, den Broeder N, de Jong EMGJ, den Broeder AA, van den Hoogen FHJ, Helliwell PS and Wenink MH: Comparing methotrexate monotherapy with methotrexate plus leflunomide combination therapy in psoriatic arthritis (COMPLETE-PSA): a double-blind, placebo-controlled, randomised, trial. The Lancet Rheumatology 2022; 4: 252–e261. https://doi.org/10.1016/S2665-9913(22)00028-5.
100. Alexeeva E, Horneff G and Dvoryakovskaya T: Early combination therapy with etanercept and methotrexate in JIA patients shortens the time to reach an inactive disease state and remission: results of a double-blind placebo-controlled trial. Pediatric Rheumatology 2021; 19: 5. https://doi.org/10.1186/s12969-020-00488-9
101. Daoud S and Taha MO: Design and synthesis of new JAK1 inhibitors based on sulfonamide-triazine conjugates. Current Computer-Aided Drug Design 2021; 17: 916–926. https://doi.org/10.2174/1573409916666201224152253
102. Cheng Y, Liu L, Xue Y, Zhou S and Li Y: An open-label, phase 1, randomized, three treatments, three-period,

crossover, relative bioavailability study of CC-292, a potent and orally available inhibitor of Bruton tyrosine kinase. Journal of Clinical Pharmacy and Therapeutics 2022; 47: 1186–1193. https://doi.org/10.1111/jcpt.13653

103. Gao Y, Zhang Y and Liu X: Rheumatoid arthritis: pathogenesis and therapeutic advances. Med Comm 2024; 5: 509. https://doi.org/10.1002/mco2.509
104. Choi KJ, Kim YY, Jang SY, Ahn YG, Suh KH, Kim YH and Kim HS: Synergistic effects of BTK inhibitor HM71224 and methotrexate in a collagen-induced arthritis rat model. *In-vivo* 2021; 35: 3245–3251. https://doi.org/10.21873/invivo.12619
105. Arneson LC, Carroll KJ and Ruderman EM: Bruton's tyrosine kinase inhibition for the treatment of rheumatoid arthritis. ImmunoTargets and Therapy 2021; 10: 157. https://doi.org/10.2147/ITT.S288550
106. Paliwal S, Bawa S, Shalmali N and Tonk RK: Therapeutic potential and recent progression of BTK inhibitors against rheumatoid arthritis. Chemical Biology & Drug Design 2024; 104: 14582. https://doi.org/10.1111/cbdd.14582
107. Arneson LC, Carroll KJ and Ruderman EM: Bruton's tyrosine kinase inhibition for the treatment of rheumatoid arthritis. ImmunoTargets and Therapy 2021; 10: 333–342. https://doi.org/10.2147/ITT.S288550.
108. Brullo C, Villa C, Tasso B, Russo E and Spallarossa A: BTK inhibitors: a medicinal chemistry and drug delivery perspective. International Journal of Molecular Sciences 2021; 22: 7641. https://doi.org/10.3390/ijms22147641
109. Khojasteh C, Sodhi JK and Halladay J: The past decade of Genentech experience in elucidation of novel reaction mechanisms in drug metabolism. Medicinal Chemistry Research 2023; 32: 2016–2033. https://doi.org/10.1007/s00044-023-03128-5
110. Price E, Bombardieri M, Kivitz A, Matzkies F, Gurtovaya O, Pechonkina A, Jiang W, Downie B, Mathur A, Mozaffarian A, Mozaffarian N and Gottenberg JE: Safety and efficacy of filgotinib, lanraplenib and tirabrutinib in Sjögren's syndrome: a randomized, phase 2, double-blind, placebo-controlled study. Rheumatology 2022; 61: 4797–4808. https://doi.org/10.1093/rheumatology/keac167
111. Schafer PH: Spebrutinib (CC-292) affects markers of B cell activation, chemotaxis, and osteoclasts in patients with rheumatoid arthritis: Results from a mechanistic study. Rheumatology and Therapy 2020; 7: 101. https://doi.org/10.1007/s40744-019-00182-7
112. Purvis GSD, Aranda-Tavio H, Channon KM and Greaves DR: Bruton's TK regulates myeloid cell recruitment during acute inflammation. British Journal of Pharmacology 2022; 179: 2754–2770. https://doi.org/10.1111/bph.15778
113. Zhang D, Gong H and Meng F: Recent advances in BTK inhibitors for the treatment of inflammatory and autoimmune diseases. Molecules 2021; 26: 4907. https://doi.org/10.3390/molecules26164907
114. Neys SFH, Rip J, Hendriks RW and Corneth OBJ: Bruton's tyrosine kinase inhibition as an emerging therapy in systemic autoimmune disease. Drugs 2021; 81: 1605. https://doi.org/10.1007/s40265-021-01592-0
115. Liu Y: A novel tricyclic BTK inhibitor suppresses B cell responses and osteoclastic bone erosion in rheumatoid arthritis. Acta Pharmacologica Sinica 2021; 42: 241. https://doi.org/10.1038/s41401-020-00578-0
116. De Bondt M, Renders J, Struyf S and Hellings N: Inhibitors of Bruton's tyrosine kinase as emerging therapeutic strategy in autoimmune diseases. Autoimmunity Reviews 2024; 103532.
117. Conaghan PG, Nowak M, Du S, Luo Y, Landis J, Pachai C, Fura A, Catlett IM, Grasela DM and Østergaard M: Evaluation of BMS-986142, a reversible Bruton's tyrosine kinase inhibitor, for the treatment of rheumatoid arthritis: a phase 2, randomised, double-blind, dose-ranging, placebo-controlled, adaptive design study. The Lancet Rheumatology 2023; 5: 263–e273. https://doi.org/10.1016/S2665-9913(23)00089-9
118. Watterson SH and Wisniewski SR: A twisted road to the discovery and chemical development of BMS-986142: a reversible inhibitor of BTK conformationally constrained by two rotationally stable atropisomeric axes. In: Complete Accounts of Integrated Drug Discovery and Development: Recent Examples from the Pharmaceutical Industry. Volume 4. American Chemical Society 2022: 173–202. https://doi.org/10.1021/bk-2022-1423.ch004
119. Montalban X, Wallace D and Genovese MC: Characterisation of the safety profile of evobrutinib in over 1000 patients from phase II clinical trials in multiple sclerosis, rheumatoid arthritis and systemic lupus erythematosus: an integrated safety analysis. Journal of Neurology, Neurosurgery & Psychiatry 2023; 94: 1–9.
120. Sahin Eroglu D, Dalva K, Azap A, Kutlay N, Ates A and Yuksel M: Two birds with one stone: a Bruton's tyrosine kinase inhibitor in a patient with rheumatoid arthritis and 17p+ chronic lymphocytic leukaemia. Scandinavian Journal of Rheumatology 2023; 52: 703–704. https://doi.org/10.1080/03009742.2023.2218206
121. Guehring H, Wallace D, Genovese MC, Tomic D, Parsons-Rich D, Le Bolay C, Kao A and Montalban X: Safety profile characterization of evobrutinib in over 1000 patients from phase II clinical trials in multiple sclerosis, rheumatoid arthritis and systemic lupus erythematosus (S14.007). Neurology 2022; 98(18): 3002. https://doi.org/10.1212/WNL.98.18_supplement.3002
122. Wallace DJ, Dörner T, Pisetsky DS, Sanchez-Guerrero J, Patel AC, Parsons-Rich D and Le Bolay C: Efficacy and safety of the Bruton's tyrosine kinase inhibitor evobrutinib in systemic lupus erythematosus: results of a phase II, randomized, double-blind, placebo-controlled dose-ranging trial. ACR Open Rheumatology 2023; 5: 38–48. https://doi.org/10.1002/acr2.11511
123. Beerli C: Discovery of LOU064 (Remibrutinib), a potent and highly selective covalent inhibitor of Bruton's tyrosine kinase. Journal of Medicinal Chemistry 2020; 63: 5102. https://doi.org/10.1021/acs.jmedchem.9b01916
124. Sabat M, Dougan DR, Knight B, Lawson JD, Scorah N, Smith CR and Taylor ER: Discovery of the Bruton's tyrosine kinase inhibitor clinical candidate TAK-020 (S)-5-(1-((1-acryloylpyrrolidin-3-yl)oxy)isoquinolin-3-yl)-2,4-dihydro-3H-1,2,4-triazol-3-one, by fragment-based drug design. Journal of Medicinal Chemistry 2021; 64: 12893–12902. https://doi.org/10.1021/acs.jmedchem.1c01026
125. Fleischmann R, Friedman A, Drescher E, Singhal A, Cortes-Maisonet G, Doan T and Lu W: Safety and efficacy of elsubrutinib or upadacitinib alone or in combination (ABBV-599) in patients with rheumatoid arthritis and inadequate response or intolerance to biological therapies: a multicentre, double-blind, randomised, controlled, phase 2 trial. The Lancet Rheumatology 2022; 4: 395–e406. https://doi.org/10.1016/S2665-9913(22)00092-3
126. Isenberg D, Furie R, Jones NS, Guibord P, Galanter J, Lee C and McGregor A: Efficacy, safety, and pharmacodynamic effects of the Bruton's tyrosine kinase inhibitor fenebrutinib (GDC-0853) in systemic lupus erythematosus: results of a phase II, randomized, double-blind, placebo-controlled trial. Arthritis & Rheumatology 2021; 73: 1835–1846. https://doi.org/10.1002/art.41811

127. Zhang B: Abstract CT132: Orelabrutinib, a potent and selective Bruton's tyrosine kinase inhibitor with superior safety profile and excellent PK/PD properties. Cancer Research 2020; 80(16): 132. https://doi.org/10.1158/1538-7445.AM2020-CT132
128. Akasaka D: Novel Bruton's tyrosine kinase inhibitor TAS5315 suppresses the progression of inflammation and joint destruction in rodent collagen-induced arthritis. PLoS One 2023; 18: 0282117. https://doi.org/10.1371/journal.pone.0282117
129. Takeuchi T, Tanaka S, Murata M and Tanaka Y: Irreversible covalent Bruton's tyrosine kinase inhibitor, TAS5315 versus placebo in rheumatoid arthritis patients with inadequate response to methotrexate: a randomised, double-blind, phase IIa trial. Annals of the Rheumatic Diseases 2023; 82: 1025–1034. https://doi.org/10.1136/ard-2022-223759
130. Worth C, Al-Mossawi MH, Macdonald J, Fisher BA, Chan A, Sengupta R, Packham J, Gaffney K, Gullick N, Cook JA and Corn TH: Granulocyte-macrophage colony-stimulating factor neutralisation in patients with axial spondyloarthritis in the UK (NAMASTE): a randomised, double-blind, placebo-controlled, phase 2 trial. The Lancet Rheumatology 2024; 6: 537–545. https://doi.org/10.1016/S2665-9913(24)00099-7
131. Yao X, Ren Y, Zhao Q, Chen X, Jiang J, Liu D and Hu P: Pharmacokinetics analysis based on target-mediated drug distribution for RC18, a novel BLyS/APRIL fusion protein to treat systemic lupus erythematosus and rheumatoid arthritis. European Journal of Pharmaceutical Sciences 2021; 159: 105704. https://doi.org/10.1016/j.ejps.2021.105704
132. Lv X, Wang L, Zou X and Huang S: Umbilical cord mesenchymal stem cell therapy for regenerative treatment of rheumatoid arthritis: opportunities and challenges. Drug Design, Development and Therapy 2021; 15: 3927–3936. https://doi.org/10.2147/DDDT.S323107
133. Sarsenova M, Issabekova A, Abisheva S, Rutskaya-Moroshan K, Ogay V and Saparov A: Mesenchymal stem cell-based therapy for rheumatoid arthritis. International Journal of Molecular Sciences 2021; 22: 11592. https://doi.org/10.3390/ijms222111592
134. Liu D, Che X, Wang X, Ma C and Wu G: Tumor vaccines: unleashing the power of the immune system to fight cancer. Pharmaceuticals 2023; 16: 1384. https://doi.org/10.3390/ph16101384
135. Zimmerman DH: Current status of immunological therapies for rheumatoid arthritis with a focus on antigen-specific therapeutic vaccines. Frontiers in Immunology 2024; 15: 1. https://doi.org/10.3389/fimmu.2024.1334281
136. Pulendran B, Arunachalam PS and O'Hagan DT: Emerging concepts in the science of vaccine adjuvants. Nature Reviews Drug Discovery 2021; 20: 734. https://doi.org/10.1038/s41573-021-00163-y
137. Sonigra A: Randomized phase I trial of antigen-specific tolerizing immunotherapy with peptide/calcitriol liposomes in ACPA+ rheumatoid arthritis. JCI Insight 2022; 7: 160964. https://doi.org/10.1172/jci.insight.160964
138. Abuelazm M, Ghanem A, Mahmoud A and Brakat AM: The efficacy and safety of olokizumab for rheumatoid arthritis: A systematic review, pairwise, and network meta-analysis. Clinical Rheumatology 2023; 42: 1503. https://doi.org/10.1007/s10067-023-06519-6
139. Feist E: Olokizumab plus methotrexate: Safety and efficacy over 106 weeks of treatment patient disposition. Annals of the Rheumatic Diseases 2024; 83: 1454. https://doi.org/10.1136/ard-2023-225473

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